Protocol Title:
Multicenter Trial of Combined Pharmacotherapy to Treat Cocaine Dependence

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6698

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03/07/2013

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01/04/2018

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Co-Investigator(s):
John Mariani, MD

Research Chief:
Herbert Kleber, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
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 Pennsylvania). Kyle Kampman, MD is the Principal Investigator at the University of Pennsylvania site.

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
This study was a collaborative study between the Substance Treatment and Research Service (STARS) and the University of Pennsylvania (UPenn) with one uniform screening and study procedure. In total, 169 individuals were enrolled, 127 were randomized, and 83 (65%) completed the study. Of the individuals enrolled at the STARS site, 89 participants were enrolled, with 68 being randomized. Thirty-seven participants (54%) completed the 14-week treatment trial. The retention is what is expected in this population and kept us on track for investigating both the primary and secondary aims of the investigation. Patients on average experienced the study as helpful and informative. The study procedures were well tolerated by participants. We are working on cleaning the data for analysis.

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 occuring 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 occured 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)
12/31/2021

Overall Progress

Approved sample size
99
Total number of participants enrolled to date
89
Number of participants who have completed the study to date
37
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
cocaine dependent adults
Total number of participants enrolled from this population to date
89
Gender, Racial and Ethnic Breakdown
Seventy-one (80%) out of 89 subjects enrolled for this study were male, 18 (20%) were Caucasian, 36 (41%) were African-American, 24 (27%) were Hispanic, 3 (3%) were Asian, 2 (2%) were Native American, and 6 (7%) were Other.

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
1
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 due to no longer being interested in treatment.

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
- ✓ 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
- ✓ Substance Users

Research Support/Funding

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

Souce of funding: Multicenter Trial of Combined Pharmacotherapy to Treat Cocaine Dependence

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
Multicenter Trial of Combined Pharmacotherapy to Treat Cocaine Dependence
Grant Number
1R01DA033310-01A1

Select one of the following
Multicenter(NYSPI is the lead 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
✓ 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 multi-site double-blind, placebo-controlled outpatient study of the safety and efficacy of Adderall-XR (MAS-ER) and topiramate in the treatment of cocaine dependence. At this site we plan to enroll 99 and randomized 88 subjects in a 14-week trial. The primary objective of the study is to determine the efficacy of MAS-ER and topiramate in promoting cocaine abstinence among cocaine-dependent patients.

Background, Significance and Rationale

Background, Significance and Rationale

To date, there are no proven pharmacotherapies for cocaine dependence. Cocaine dependence is associated with dysregulated dopamine transmission. We hypothesized that the combination of an agent that increased baseline dopamine signaling (amphetamine) with one that reduced cocaine-induced dopamine release (topiramate) would improve dopamine regulation and be associated with improved cocaine use outcomes. We conducted a pilot randomized double-blind placebo-controlled trial of extended–release mixed amphetamine salts (MAS-ER) combined with topiramate for the treatment of cocaine dependence that demonstrated a significant interaction between treatment and baseline use, with the combination

pharmacotherapy more effective for higher frequency users of cocaine. The proposed project aims to confirm these results in a large-scale two-site clinical trial.

There is no clearly effective pharmacotherapy for cocaine dependence and clinical trials of medications for cocaine dependence have mainly tested the administration of a single agent. The proposed project builds on our promising pilot data (see preliminary studies) testing the novel combination of mixed amphetamine salts extended-release (MAS-ER) and topiramate as a treatment for cocaine dependence. The hypothesis underlying this approach is that MAS-ER and topiramate corrects dopamine dysregulation associated with cocaine dependence by simultaneously increasing dopamine transmission and reducing cocaine-induced dopamine release, thus both decreasing baseline craving and cocaine-induced reinforcement. Using a combination of medications with different putative mechanisms of effect on the neuropharmacology of cocaine dependence is a novel treatment strategy for cocaine dependence. If the present trial confirms the promising pilot data (Mariani et al., 2012), this could significantly shift the paradigm for cocaine medications development and clinical practice, by encouraging development of rational combinations of medications that might have more potent effects than individual medications.

In addition, while the proposed clinical trial primarily employs standard methods for testing cocaine dependence pharmacotherapies, innovative elements of the design, such as providing voucher incentives for study visit attendance and medication bottle return, as well as the use of a supportive medication adherence-focused psychosocial therapy, represent an advance in the state of the art of cocaine dependence pharmacotherapy trials. Poor adherence to study medications threatens the internal validity of clinical trials and has likely been a significant impediment to cocaine medication development. These design innovations were successful in our pilot study and resulted in superior retention and medication adherence rates, suggesting that procedures such as those implemented here may be of broad value for improving clinical trials in this field.

Specific Aims and Hypotheses

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

Primary Hypothesis: The proportion of participants achieving sustained cocaine abstinence for three consecutive weeks at the end of the study will be significantly greater for the combined pharmacotherapies group compared to the placebo group.

Hypothesis 2: The proportion of participants achieving sustained cocaine abstinence for three consecutive weeks during any three consecutive weeks of the study will be significantly greater for the combined pharmacotherapies group compared to the placebo group.

Hypothesis 3: The proportion of urine samples negative for cocaine metabolites will be greater in the combined pharmacotherapies group compared to the placebo group.

Specific Aim 2: To determine the effect of MAS-ER and topiramate on cocaine withdrawal symptoms and craving among cocaine-dependent patients.

Hypothesis 4: Cocaine withdrawal symptoms will be reduced to a greater degree in the combined pharmacotherapies group compared to the placebo group as measured by the Cocaine Selective Severity

Assessment (CSSA).

Hypothesis 5: Cocaine craving symptoms will be reduced to a greater degree in the combined pharmacotherapies group compared to the placebo group as measured by the Brief Substance Craving Scale (BSCS).

Description of Subject Population

Sample #1

Specify subject population
Adult Cocaine Dependent Individuals
Number of completers required to accomplish study aims
62
Projected number of subjects who will be enrolled to obtain required number of completers
99
Age range of subject population
18-60

Gender, Racial 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 99 participants into the study who meet eligibility criteria.

Recruitment Procedures

Describe settings where recruitment will occur
The Project is a multi-site trial (Columbia University and University of Pennsylvania). 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.
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 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.

The proposed project will also be conducted at the University of Pennsylvania's Treatment Research Center (TRC). The TRC is a community-based outpatient addiction treatment-research program that is part of the University of Pennsylvania Center for the Study of Addictions (Dr. Charles P. O'Brien, Director). The TRC offers outpatient addiction treatment for individuals from the greater Philadelphia area who are seeking treatment for their addiction and who qualify for one of the grant-sponsored treatment studies on alcohol, cocaine, dual cocaine-alcohol, heroin or nicotine dependence. Subject recruitment is ongoing and accomplished through community, professional, and self-referrals from the greater metropolitan Philadelphia area.

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
01811940

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

CRITERION	METHOD OF ASCERTAINMENT
Inclusion:	
1. Men and women between the ages of 18-60 who meet DSM-IV criteria for current cocaine dependence (DSM-IV-TR).	1. MINI; demographic information
2. Used cocaine at least 9 days in the past 28 days, with at least weekly cocaine use	2. Subject self-report; urine drug screen
3. Individuals must be capable of giving informed consent and capable of complying with study procedures.	3. Initial contact interview

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

Exclusion:	
1. Meets DSM-IV-TR criteria for bipolar disorder, schizophrenia or any psychotic disorder other than transient psychosis due to drug abuse.	1. MINI
2. Individuals with any current Axis I psychiatric disorder as defined by DSM-IV-TR supported by the MINI that in the investigator's judgment are unstable, would be disrupted by study medication, or are likely to require pharmacotherapy or psychotherapy during the study period. Individuals who are currently stable on a psychotropic medication for at least 3 months may be included if in the investigator's opinion the psychotropic	2. MINI,psychiatric evaluation

medication the patient is taking is compatible with the study medication (mixed amphetamine salts plus topiramate) and does not entail serious risk of adverse effects from the drug interactions. Individuals cannot be on any psychostimulants or other contraindicated medications.	
3. Individuals with a history of seizures or unexplained loss of consciousness	3. Medical history
4. History of allergic reaction to candidate medications (amphetamine or topiramate).	4. Medical history
5. Individuals with significant current suicidal risk.	5. MINI; psychiatric evaluation
6. Women who are pregnant, nursing, or failure in sexually active female patients to use adequate contraceptive methods.	6. Self-report, urinary HCG
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.	7. Medical history, physical examination and laboratory tests.
8. 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.	8. Medical history including a cardiovascular risk profile and ECG
9. Individuals with use of carbonic anhydrase inhibitors	9. Self-report
10. History of glaucoma	10. Self-report
11. History of kidney stones	11. Self-report
12. Use of drugs that may be additive to the bicarbonate lowering effects of topiramate	12. Medical history
13. Body Mass Index (BMI) < 18kg/m2	13. Weight and height measurement

14. History of failure to respond to a previous adequate trial of either of the candidate medications for cocaine dependence	14. Self-report
15. Individuals physiologically dependent on any other drugs (excluding nicotine or cannabis) which require medical intervention	15. MINI; psychiatric evaluation
16. Individuals who are legally mandated (e.g., to avoid incarceration, monetary or other penalties, etc.) to participate in substance abuse treatment program	16. Self-report
17. Individuals with a current history (within the past 6 months) of amphetamine abuse or dependence, including amphetamines such as methamphetamine and MDMA.	17. MINI

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
Brezing, Christina, MD
Dakwar, Elias, MD
Evans, Elizabeth, MD
Levin, Frances, MD
Luo, Sean, MD
Mariani, John, MD
Marino, Leslie, MD
Nunes, Edward, MD
Shulman, Matisyahu, MD
Vaezazizi, Leila
Williams, Arthur
Type in the name(s) not found in the above list

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.

Suzette M. Evans, Ph.D.: Psychologist with 22 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 10 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., Adam Bisaga, M.D., John Mariani, M.D., Elias Dakwar, M.D., Nasir Naqvi, M.D. PhD., Elizabeth Evans, M.D., Christina Brezing, M.D., Sean Luo, M.D., PhD., Arthur Williams, M.D., Leslie Marino, M.D., Edward Nunes, M.D., **Matisyahu Shulman, MD, and Leila Vaez-Azizi, MD**). 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. The psychiatrist will review all medications the participant is currently taking and discuss potential interactions between these medications and the study medications (mixed amphetamine salts plus topiramate). This discussion will be documented in the clinical chart. 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., Daniel Brooks, M.A., Payal Pandya, M.A., and Kaitlyn Mishlen, M.A.) 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 (Marisa Savic, 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., Daniel Brooks, M.A., Payal Pandya, M.A., Kaitlyn Mishlen, M.A. 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, Dakwar, Naqvi, Evans, Brezing, Lou, Williams, Marino, Nunes, **Shulman, and Vaez-Azizi**), who have extensive experience with individuals with substance use disorders in treatment settings.

b. Drug Administration: Extended-release mixed amphetamine salts (MAS-ER), topiramate 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, Dakwar, Naqvi, Evans, Brezing, Lou, Williams, Marino, Nunes, **Shulman, and Vaez-Azizi**) 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., Daniel Brooks, M.A., Payal Pandya, M.A., and Kaitlyn Mishlen, M.A.) under the supervision of Dr. Carpenter.

General Design:
99 subjects whom meet criteria for 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 MAS-ER and topiramate. Table 1 shows the overall design.

1. Design Overview
This proposal will test the hypothesis that MAS-ER and topiramate will promote cocaine abstinence. The study will have 1-week single-blind placebo lead-in phase and participants who are abstinent during this week, or noncompliant with study procedures, will not be randomized. After completion of the lead-in period (week 1), individuals will be randomized to MAS-ER and topiramate or placebo. Participants who are randomized to the combination medication arm will have their dose titrated to 60 mg MAS-ER daily (over 2 weeks) and 200 mg topiramate a day (over 6 weeks) and maintained on this dose through week 13 of the trial. During week 14, participants will be tapered off both medications (see Table 1. below). All participants will receive a supportive behavioral treatment that emphasizes study procedure adherence (Anton et al 2006; Johnson et al 2003b). Starting in week one, all patients will receive incentives for compliance with study procedures on an escalating reinforcement schedule similar to that developed previously (Budney et al 2000; 2006) and not contingent on urine results. During week 14 patients assigned to active medication have their medication tapered. The purpose of the lead-out is to blind patients to the exact point of medication discontinuation and to provide naturalistic data on the effects of medication discontinuation. Moreover, a 3 month follow-up will be conducted to determine what happens to cocaine use after treatment discontinuation. The study design is diagrammed in Table 1.

Single-Blind PBO Lead-In Phase: Participants who meet inclusion criteria and who sign informed consent will be placed 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. Individuals will be stratified by the site (Columbia versus University of Pennsylvania) and the presence of an alcohol use disorder. The purpose of the stratification is to distribute these potential prognostic factors equally across treatment groups. To the extent that these stratification variables are predictive of outcome, stratifying by them should enhance statistical power to test treatment effects (Fleiss et al 1986).

Randomization: Those patients randomized to the placebo group will continue to receive placebo throughout the treatment. Patients randomized to the MAS-ER/topiramate group will begin receiving both medications at the start of week 2 and will receive a stable dose of MAS-ER by study week 4 and topiramate by week 8. Dosing Schedule: Subjects will take capsules (PBO or ER-MAS/topiramate) as titrated in Table 2 below. Medication Lead-out: During week 14 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.

26 Week Outcome: Twelve weeks after study completion (26 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 26 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.

Medications: MAS-ER, topiramate 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. A similar approach will be used at the University of Pennsylvania pharmacy. However, there will be central randomization at the Columbia pharmacy. 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, topiramate or matching placebo will be given in a fixed-flexible dose schedule with the MAS-ER dose titrated to 60 mg per day, the topiramate dose titrated to 200 mg per day or the maximum tolerated dose.

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 12.5 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.

Currently the study is run under the NYS Controlled Substance license # 0400081 held by the NYS OMH and the DEA Researcher Registration # PN0093461 held by the NYSPI Pharmacy Department. As soon as the PI, Dr. Frances R. Levin, obtains her own NYS Controlled Substance license and DEA Researcher Registration # the projects will be run under both her researcher specific NYS license, her DEA Researcher Registration and the NYS/OMH license and NYSPI DEA Researcher Registration.

The drug stock of controlled substances for each project will be ordered, maintained and prepared under the Institutional registration at the NYSPI Pharmacy (OMH/NYS Controlled Substance license # 0400081). Packaged drugs (kits) will be transferred to the Principal Investigator (Dr. Frances R. Levin) using a DEA 222 form with the address where the study will take place (e.g. 3 Columbus Circle, Suite 1403, NY, NY 10019). Drugs or kits for individual patients will be transferred from the Institutional registration (#0400081) to the investigator registration using DEA 222 forms and transported by Marcia Loughran, FNP (supervisor of controlled substance activity) to the 3 Columbus Circle Suite 1403, NY, NY 10019 research

site. Drug will then be kept in the wall mounted, double-door, double-locked storage cabinets at 3 Columbus Circle until it is given to the participant.

Topiramate (25 mg and 100 mg tablets) will be packaged in gelatin capsules with lactose filler plus 12.5 mg of riboflavin marker. Placebo will consist of matching gelatin capsules with lactose filler and 12.5 mg of riboflavin. Topiramate will be started at the beginning of week 2 concurrent with the initiating of ER-MAS titration. Because rapid titration of topiramate is associated with greater likelihood of side effects, (e.g., cognitive effects), topiramate will be increased slowly over a period of 6 weeks to 200 mg. Topiramate or matching placebo will be given on a fixed-flexible schedule, titrated to 200 mg, as follows: Week 2(Days 8-14): 25 mg at night; Week 3 (Days 15-21): 25 mg twice a day; Week 4 (Days 22-28): 25 mg in the morning and 50 mg in the evening; Week 5(Days 29-35): 50 mg twice a day; Week 6(Day 36-42): 75 mg twice a day; Week 7 (Days 43-49): 75 mg in the morning and 100 mg in the evening; Week 8 (Day 50 and through the end of study): 100 mg twice a day. Since topiramate will be administered twice a day, all patients will receive capsules in the morning and evening. The 2 medications will be color-coded such that if the dose of one of the medications needs to be titrated up or down, the patient and psychiatrist will be able to easily monitor this. However, the placebo medications will also be "color-coded" and matched to the colors used for the active medications. Topiramate is FDA approved for the treatment of epilepsy in doses of up to 400 mg per day, which is recommended to be titrated over a 6-week period. The planned titration of topiramate over 6-weeks to a maximum dose of 200mg/day allows us to achieve this targeted dose as quickly as possible without sacrificing tolerability.

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 10 mg/day of MAS-ER or 25 mg/day topiramate, 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 and topiramate.

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 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.

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 for riboflavin. The patient will consume up to approximately 65 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 non-childproof packaging. In the event that participants miss four consecutive days of medication, they will be given half the dose until their next scheduled study visit.

Medical Management Psychosocial Intervention: Phase II pharmacotherapy clinical trials should employ a psychosocial intervention to promote adherence to the study medication regimen and study visit schedule, without inflating the placebo response rate. The psychosocial intervention for this study will be Medical Management used for Project COMBINE (Anton et al., 2006), modified for cocaine dependence. All participants will have a manual-guided (Pettinati et al., 2005) supportive behavioral treatment session with the research psychiatrist each week. This psychosocial intervention facilitates compliance with study medication and other study procedures, promotes abstinence from marijuana and other substances, and encourages mutual-support group attendance. Dr. Mariani will provide ongoing supervision to other study physicians to prevent therapeutic drift. All study psychiatrists will be trained in providing Medical Management and refresher training sessions will be provided every 6 months. As director of Columbia's Substance Treatment and Research Service, Dr. Mariani has extensive experience conducting and supervising Medical Management and other similar medication adherence focused psychosocial intervention models. Our research group recently completed a 12-week cocaine dependence pharmacotherapy trial that employed a medication adherence-focused psychosocial intervention similar to Medical Management had an overall retention rate of 72%.

Patient Payments: During screening, potential participants will receive $5 for each screening visit and $25 for completion of the screening process. A voucher incentive system will be used to compensate patients for their time and travel and to encourage compliance with study procedures (visits and ratings). Weekly return of medication bottles will receive $10 each week. Further, patients will be paid $30 for the completion of assessments at the end of study visit at week 14 and $50 for completion of assessments at a follow-up appointment conducted 26 weeks after randomization.

Once entered into the study, patient can earn weekly cash payments if they come to their study appointments, complete the required assessments, and provide a urine sample at each visit. The payment 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 payment back to their initial $0.50 from which the cash can escalate again according to the same schedule. Attending three consecutive clinic visits following non-attendance will return the payment to the level achieved prior to the missed visit. To further reinforce continued attendance, patients will earn $10 in cash each week for returning their pill bottles and any remaining medication for that week. The payment for pill bottle return is only contingent on returning the pill bottle and any remaining pills, not for taking the medication. If an individual attends all visits, s/he could potentially earn a total of $621.50 over a 14 week period for attending study visits and completing required assessments. The weekly cash value given will be less than $120, with $116.50 being the most potentially earned at week 14. We believe that this modest reinforcement schedule improves retention and return of medication bottles to enhance pill counts. In our recently completed pilot trial with topiramate and MAS-ER, 79% completed the maintenance phase of the trial. While we do not have definitive data regarding the superiority of this approach over no vouchers, the potential benefits of having less missing data and higher treatment retention outweigh the modest cost of this approach.

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. 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 week 4 of the trial. An ECG and clinical blood work will also be repeated at the end of the study. 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. 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 for riboflavin which will 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

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 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 $\geq$ 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 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 $\geq$ 6 [much worse than baseline] for two consecutive weeks).

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), and blood pregnancy test for women). They may be repeated during the study if clinically indicated. A blood sample (10 ml) for topiramate levels and electrolytes will be taken in weeks 5, 9 and 13. Approximately, 70 ml of blood will be drawn overall (i.e., baseline and study completion = 2 x 20 ml =40 ml /topiramate levels 3 x 10 ml= 30 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.

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:
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). An ECG will be repeated at week 4 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 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).

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
2

Drug #1

Name of the drug

Topiramate
Manufacturer and other information

Other name: Topamax
Manufacturer: Ortho-McNeil

Approval Status
IND is approved
IND#
76, 166
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Levin, Frances, MD

Drug #2

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#
76, 166
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 medical management therapy within 2 weeks after the initial screening evaluation. Medical management therapy is an abstinence-focused supportive psychotherapy condition developed for substance use disorder pharmacotherapy clinical trials. Medical management therapy approximates the level of support of abstinence that patients would expect to receive in community

treatment (general support of abstinence, tying improvement to reduction or cessation of drug use, referral to 12-step programs, etc.)
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 medical management therapy until 2-3 weeks after their initial screening evaluation for the study. Medical management therapy will start during the single-blind lead-in phase.
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, 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, cognitive-behavioral therapy, 12-step facilitation, and other methods. Alternatives treatment settings for substance abuse include drug free outpatient treatment, inpatient detoxification, or residential treatment. Patients are informed that they may request referral for other treatment options.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

1. Risks

The major risk of research participation is related to drug administration. Although the maximal dose for topiramate is 400 mg/day, it will be administered in this study in doses of up to 200 mg/day. Clinical studies and post-marketing reports have revealed a number of adverse reactions. These events were generally mild to moderate and occurred early in therapy. Adverse events most often associated with the use of topiramate can be classified into 2 general categories: 1) psychomotor slowing, difficulty with concentration, and speech and language problems, in particular word-finding difficulties, and 2) somnolence or fatigue. Somnolence and fatigue were the most frequently reported adverse events during clinical trials with topiramate. 1.5% of adults exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2-4 times than expected in similar, untreated populations. Metabolic acidosis (decreased bicarbonate in the blood) may be associated with topiramate treatment. Metabolic acidosis can result in thinning of the bones (osteoporosis) with an increased risk for fractures. Metabolic acidosis may increase the risk for kidney stones. Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common side effect of topiramate. Some clinical trials have observed that patients treated with topiramate may experience weight loss. Therefore, BMI will be monitored closely during the

study dose adjustments will be made if necessary. The long-term risks of topiramate are not yet known. Topiramate is of unknown risk to a fetus.

MAS-ER has been approved for maximal use of up to 60 mg/day. Adverse events most commonly associated with amphetamine administration include: decreased appetite, decreased weight, headache, stomachache and insomnia. Rare side effects include severe hypertension, seizures, psychosis, mania and, myocardial infarction. Although it is possible that the side effects of each of the medications may be worsened by co-administration of the 2 medications, it may be more likely that the side effects of associated with each medication will not be additive. 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). Urine pregnancy tests will be evaluated at baseline and monthly 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 the previous trial adverse events most commonly experienced by individuals on the combination of the two medications were insomnia and increased/decreased appetite. Other common side effects included fatigue, GI upset, headache, nausea, dizziness, body ache, dry mouth, anxiety, irritability, paresthesia, cold/flu, somnolence, hyperactivity/jitteriness, diarrhea, disorientation, and itching. Rare side effects in the previous trial were chest pains, depression, rash, vomiting, cough, sore throat, distracted, racing heart, memory loss, fever, and tooth infection.

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).

One side effect common to both medications is weight loss. Therefore, BMI will be monitored closely during the study and dose adjustments will be made if necessary. For both medications, 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) and topiramate has been studied in cocaine-dependent patients without reports of adverse events (Kampman, 2004) In our recently completed, published pilot trial, the combination of the 2 medications was well-tolerated, even in the presence of continued cocaine use (Mariani et al., 2012). Although both medications have been well-tolerated when administered to cocaine-dependent individuals, we cannot be absolutely certain that their side effect profiles will remain the same when co-administered with cocaine. The interactions between amphetamines, topiramate and 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 topiramate and amphetamines would alter these risks. Therefore, patients with histories of convulsions or heart disease will be excluded. Although MAS-ER is usually, if anything, activating, topiramate may counter this effect and the combination may lead to an overall sedation and therefore increased sedation or intoxication could be experienced if topiramate is combined with other sedating drugs or alcohol. Patients will be informed about the common side effects of both MAS-ER and topiramate and warned about the possibility of interactions between these medications and cocaine or other drugs.

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

Topiramate and MAS-ER is of unknown risk to a fetus. Female participants will be required to use effective methods of birth control (i.e., condom with spermicide, diaphragm with spermicide, birth control pills). Urine pregnancy tests will be evaluated at baseline and monthly throughout the trial. If a patient does become pregnant, she will be withdrawn from study medication and will be offered continued non-pharmacological treatment at the clinic.

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.

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.

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 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 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 and will contain riboflavin. Patients who are found to abuse/divert their study medication will be taken off their study medication.

Describe procedures for minimizing risks

Procedures for Risk Minimization
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 or topiramate 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 (26 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 26 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 and Safety Monitoring Plan

Patients are closely monitored throughout the trial as described above. Drs. Levin and Kampman, the Principal Investigators on this study will be responsible for data and safety monitoring throughout the trial. 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. Steve Donovan, Deborah Haller, and Soteri Polydorou. They will review data provided by the Principal Investigators on an annual basis to assess the recruitment, progress, safety, adverse events, and serious adverse events associated with the study. Individuals on the Safety Monitoring Committee 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" with one group 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.

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 study medications with cocaine or with other street drugs or alcohol. Patients will give informed consent before entering the study and will be re-consented between weeks 6-8 regarding the anticipated risks and benefits of medication treatment. 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 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 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 $5 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 $40 for completing the screening process. Patients will also be reimbursed $5 for transportation at each study visit.

In some instances when patients take alternative transportation (i.e. driving to the clinic) they will be reimbursed up to $20.00 in cash if they provide receipts for expenses such as tolls and parking. As described above, patients can earn cash payments at the end of each week 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 a total of $621.50 over 14 weeks. The weekly cash value given will be less than $120, with $116.50 being the most potentially earned at week 14.

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