Study: # 7280 entitled Treatment of Cannabis Use Disorder among adults with co-morbid Attention-Deficit/Hyperactivity Disorder

PI: Frances R. Levin

NCT# NCT02803229

Study Protocol Date: June 07, 2016

New York State Psychiatric Institute

Institutional Review Board

June 7, 2016

To: Dr. Frances R. Levin

From: Dr. Edward Nunes, Co-Chairman
Dr. Laurence Greenhill, Co-Chairman

Subject: **APPROVAL NOTICE**

Your protocol #**7280** entitled: **TREATMENT OF CANNABIS USE DISORDER AMONG ADULTS WITH COMORBID ATTENTION-DEFICIT/HYPERACTIVITY DISORDER** (version date 06-07-16) and consent form have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **June 7, 2016 to April 3, 2017** (Reviewed by the Full Board on 04-04-16)**.**

Consent requirements:

☐ Not applicable

☐ 45CFR46.116(d) waiver or alteration of consent for the telephone interview

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

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

Approved for recruitment of subjects who lack capacity to consent: **X** No ☐ Yes

Field Monitoring Requirements: X Routine ☐ Special:

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

Enc: CF, HIPAA form

CC: RFMH Business Office (U54DA037842-01)
CU Grants & Contracts
CUMC-IRB

EN/LG/Scr

Signed copy on file at IRB

Protocol Title:
Treatment of Cannabis Use Disorder among Adults with Comorbid Attention-Deficit/Hyperactivity Disorder

Version Date:
06/07/2016

Protocol Number:
7280

Clinic:
Substance Treatment And Research Services (STARS)

First Approval:
06/07/2016

Expiration Date:
04/03/2017

Principal Investigator:
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Co-Investigator(s):
John Mariani, MD

Research Chief:
Frances Levin, MD

Cover Sheet

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

Division & Personnel

Division

What Division/Department does the PI belong to?
Substance 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.
This project is a single-site trial.

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
✓ 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
U54DA037842-01 Shared Pharmacotherapeutic Strategies for Cannabinoid & Opioid Use Disorders
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
Shared Pharmacotherapeutic Strategies for Cannabinoid & Opioid Use Disorders

Grant Number
U54DA037842-01
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
Columbia University

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations
Yes
✓ Hospital, clinics and other healthcare facilities

Hospitals,clinics and other healthcare facilities

Select from the list
or type in location(s)..
STARS at Columbia University, 3 Columbus Circle, 14th floor, Suite 1403

Lay Summary of Proposed Research

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The proposed protocol is a double-blind, placebo-controlled outpatient study of the safety and benefit of Extended-release mixed amphetamine salt (Adderall-XR, MAS-XR) in the treatment of individuals with CUD and ADHD. We plan to randomize 40 patients in a 12-week trial. The primary objective of the study is to determine the efficacy of MAS-XR in promoting cannabis abstinence among individuals with CUD and in promoting a decrease of ADHD symptoms.

Background, Significance and Rationale

Background, Significance and Rationale
ADHD is common in substance use disorder patients in general and cannabis use disorder (CUD) in

particular, occurring at rates substantially greater than in the general population. A meta-analysis found that approximately 23% of substance abusers seeking treatment have childhood and/or adult ADHD. Moreover, ADHD was overrepresented in adults with CUD compared to other substance use disorder patients seeking treatment. The importance in treating CUD individuals who also have ADHD is underscored by findings demonstrating that individuals with co-occurring ADHD and substance use disorders are a particularly intractable group: they exhibit earlier onset of use, more severe use, a more complicated pattern of remission/relapse, and poorer treatment outcomes relative to those without ADHD. Yet, to date, ADHD individuals with CUD have not been adequately studied. We have found that in our treatment research studies targeting cannabis dependence that a substantial percentage (35%) have screened positive for adult ADHD, rates that are higher than participants in our cocaine use disorder clinical trial and almost 8x greater than rates found in the general population (Kessler et al., 2006; Volkow et al., 2014). Thus, this appears to be a sizable cannabis-abusing group warranting much greater clinical attention than they are currently receiving.

While numerous studies have found that greater impulsivity is associated with poorer treatment outcome, particularly among those with ADHD, we will explore whether reduction in impulsivity is associated with less marijuana use. Further, we will assess sleep quality, a factor that might degrade the positive effects of medication treatment. While the administration of stimulants to active substance abusers remains controversial, a growing literature demonstrate that they can be given safely and at higher doses are effective in treating ADHD and stimulant use disorders. We would contend that if this study produces promising results, it will help be innovative in that it will inform clinical practice among a significant subgroup of patients seeking treatment for their CUD.

This proposal would be, to our knowledge, the first pharmacologic trial targeting individuals with CUD who also have ADHD, a group that represents approximately one-third of CUD individuals seeking treatment. The goal is to demonstrate feasibility, tolerability, and estimate effect size for purposes of planning future more definitive trials. Because of our team's extensive experience in working with stimulant medication in treating ADHD in cocaine-dependent populations, the large effect size of amphetamine in treating adult ADHD, and notable reduction in cocaine use and ADHD symptoms in cocaine-dependent ADHD adults, we will explore the efficacy of Adderall-XR (MAS-XR) for the treatment of cannabis use disorder and ADHD.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
Primary Aim: To determine among CUD individuals with ADHD whether MAS-XR is superior to placebo in: 1) promoting abstinence from cannabis use, and 2) reducing ADHD symptoms by at least 30% at the end of the maintenance phase.

- **Primary Hypothesis**: MAS-XR will be superior to placebo in promoting consecutive abstinence from marijuana use in the last 2 weeks of the study.
- **Hypothesis 2**: MAS-XR will be superior to placebo in promoting a 30% decrease of ADHD symptoms at the end of the study. The effect of treatment on both primary outcomes will be examined using logistic regressions adjusted for appropriate covariates which are known to be associated with each of the primary outcomes, respectively.

Secondary Aim: To determine if MAS-XR is superior to placebo in secondary outcomes across key domains including: 1) other cannabis use outcomes; 2) other ADHD outcome measures; 3) neuropsychological traits associated with ADHD and substance use disorder, including measures of attention, memory, and impulsivity; 4) psychosocial functioning and mood outcomes; and 5) tolerability and retention.

- **Hypothesis 3**: Treatment will be superior to placebo in: a) reducing quantity of marijuana use, b) reducing the mean number of using days per week, and c) reducing symptoms of THC withdrawal.
- **Hypothesis 4**: Treatment will be superior to placebo in: a) reducing the percentage of individuals with CGI≤ 2, b) reducing the mean change from baseline in CAARS and AISRS
- **Hypothesis 5**: Treatment will be superior to placebo in reducing deficits in neuropsychological measures of impulsivity and attention
- **Hypothesis 6**: Treatment will be superior to placebo in: a) improving psychosocial functioning and quality of life, and b) reducing mood scores
- **Hypothesis 7**: Treatment will be superior to placebo in: a) participant retention and b) increasing time to drop-out. Patients in treatment will achieve a c) maximum tolerated dose of 80 mg on average, and d) will only demonstrate mild to moderate side effects. The secondary hypothesizes will be analyzed using generalized mixed effect models with appropriate link function (identity for continuous outcomes, binary for dichotomous outcomes), where participant will be treated as a random factor. Longitudinal outcomes will be analyzed similarly with generalized mixed effect models with time as fixed effect and GEE structure to model the within participant over-time correlations as autoregressive AR(1) process. Time to dropout will be analyzed using survival analyses and Kaplan-Meier method.

To test the hypothesis related to tolerability outcome, an average maximum tolerated dose achieved across all participants will be computed with appropriate 95% confidence interval. If the confidence interval includes 80 mg, we can conclude that the average overall achieved maximum dose is not significantly different than desired 80 mg. Similar analyses will be carried out for side effect outcomes.

Exploratory Aim: We will explore whether the reduction in ADHD symptoms (e.g. impulsivity, inattention) and sleep quality mediates the effect of treatment on cannabis use.

- **Exploratory mediation hypothesis**: Reduction in ADHD symptoms, change in impulsivity, change in sleep quality and other cognitive deficits will be tested as mediators of the relationship between treatment and cannabis use using the Baron and Kenny mediation framework.

Description of Subject Population

Sample #1

Specify subject population

Adults with CUD and ADHD
Number of completers required to accomplish study aims
25
Projected number of subjects who will be enrolled to obtain required number of completers
50
Age range of subject population
18-65

Gender, Racial and Ethnic Breakdown
We plan to randomization 40 participants into the study. Both males and females will be recruited. All eligible participants are accepted; however, past experience with recruitment for cannabis dependence suggests that the approximate gender distribution for this study will likely be 20% female and 80% male. Previous and ongoing marijuana studies at STARS have had samples comprised of approximately 50% Caucasians, and 50% ethnic minorities distributed as 24% African-American and 22% Hispanic-American, and 4% other. 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 50 participants into the study who meet criteria for current CUD and ADHD.

Recruitment Procedures

Describe settings where recruitment will occur
All screening and study procedures will occur at the Substance Treatment and Research Services (STARS) of the Division on Substance Abuse (STARS Downtown) situated on 3 Columbus Circle, 14th Floor, Suite 1403, NY, NY 10019.
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 option 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 consent form.

How will the study be advertised/publicized?

We will recruit individuals with CUD and ADHD 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 CUD and ADHD will be asked to come to STARS for additional screening as per protocol #6582R. Those patients who meet criteria for CUD and ADHD and all other inclusion/exclusion criteria will be asked if they are interested in participating in the study.

Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
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
Adults with CUD and ADHD
Create or insert table to describe the inclusion criteria and methods to ascertain them

1) Individuals who meet criteria for cannabis use disorder (CUD) and report that marijuana is their primary drug of abuse	MINI; self report
2) Individuals must report using marijuana at least 5 days a week and have	Participant

a positive urine test for THC on the day of study entry	self-report; urine drug screen
3) Individuals must meet DSM-5 criteria for adult ADHD	Diagnostic Interview for ADHD in adults (DIVA)
4) Individuals who score > 22 on the AISRS scale	AISRS
5) Individuals between the ages of 18-65 capable of giving informed consent and capable of complying with study procedures	Demographics ; MD assessment
6) Women of child-bearing age will be included if they: a) are not pregnant, b) agree to use an effective method of contraception, c) agree not to become pregnant during the study and d) are not breastfeeding. To confirm this, urine pregnancy tests will be repeated every month after screening. Women will be provided a full explanation of the potential dangers of pregnancy while taking MAS-XR. If a woman becomes pregnant, she will be taken off medication and continue standard treatment at STARS. At the end of the study, patients will be offered treatment at STARS until an appropriate referral can be made to a community clinic.	Self report; urine HCG

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

1) Individuals meeting DSM-5 criteria for schizophrenia, schizoaffective illness, psychotic disorder other than transient psychosis due to drug abuse, current major depression, bipolar illness or psychiatric disorders (other than substance abuse) which require psychiatric intervention or would interfere with study participation	MINI; psychiatric evaluation
2) Individuals who are medically unstable based on laboratory tests, electrocardiogram, medical history, physical examination that would make participation hazardous	Laboratory tests; medical evaluation
3) Use of synthetic cannabinoids in the past month and meeting CUD diagnosis based on synthetic cannabinoids use alone in the past year	MINI; self report
4) Individuals with liver enzyme function tests greater than 3 times normal	Laboratory tests
5) Individuals with significant current suicidal risk	MINI; psychiatric evaluation
6) Individuals with systolic blood pressure > 140; diastolic blood pressure >90; pulse >100	Vitals assessment
7) Individuals who are cognitively impaired to impede study participation	Psychiatric evaluation
8) Nursing mothers and pregnant women	Self report; HCG
9) Individuals who are physiologically dependent on any other drugs (excluding nicotine) that would require a medical intervention	MINI; medical

	evaluation
10) Individuals with known sensitivity/allergy to MAS-XR or amphetamine analogs	Self-report; medical evaluation
11) Individuals currently being prescribed psychotropic medication (including sleep medication)	Self-report; medical evaluation
12) Individuals with history of seizures	Medical history
13) Individuals who are mandated to treatment	Self report
14) Individuals with a history of amphetamine **use disorders**, including amphetamines such as methamphetamine and MDMA.	MINI; medical evaluation
15) **Individuals with a current cocaine use disorder**	**MINI;medical evaluation**

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
Brezing, Christina, MD
Dakwar, Elias, MD
Evans, Elizabeth, MD
Levin, Frances, MD
Luo, Sean, MD
Mariani, John, MD
Marino, Leslie, MD
Naqvi, Nasir, MD
Williams, Arthur
Type in the name(s) not found in the above list
Adam Bisaga, MD

Study Procedures

Describe the procedures required for this study

General Design:
40 participants whom meet criteria for CUD and ADHD, and all other study inclusion and exclusion criteria (described above) will be randomized to the 12-week double-blind, placebo-controlled treatment trial. Patients will be randomized to receive either placebo or MAS-XR. Table 1 shows the overall design.

1. Design Overview
The proposed protocol is a double-blind, placebo-controlled outpatient study of the safety and efficacy of Adderall-XR (MAS-XR) in the treatment of individuals with CUD and ADHD. We plan to randomize 40 patients in a 12-week trial. The primary objective of the study is to determine the efficacy of MAS-XR in promoting cannabis abstinence among individuals with CUD and in promoting a decrease of ADHD symptoms. The study will have a 1-week single-blind placebo lead-in phase; 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-XR or placebo, stratified by baseline

ADHD rating, >35 or ≤35, at the end of week 1. Participants who are randomized to the medication arm will have their dose titrated to 80mg MAS-XR daily (over 2 weeks) and maintained on this dose for the subsequent 8 weeks. During week 12, participants will be tapered off of the medication (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. 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.

Medication: MAS-XR and matching placebo will be prepared by our pharmacy at the NYSPI packaged in matching gelatin capsules with lactose filler in each capsule. A PhD biostatistician at Columbia Univeristy, independent of the research team, will create the computer generated block design allociation sequence for the randomization. A non-blinded clinical psychologist at STARS allocates the randomization and informs the un-blinded NYSPI pharmacy who will then prepare the medications. 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 tolerabillity. MAS-XR or matching placebo will be given in a fixed-flexible dose schedule with the MAS-XR dose titrated to 80mg per day or the maximum tolerated dose.

This dose was based on our experience with ADHD adults with cocaine use disorder. High placebo-response rates can also obfuscate research findings. It has been our experience that even when patients have clear-cut diagnosis of ADHD, there is a subset of individuals who self-report ADHD improvement early on in treatment, prior to medication administration. Therefore, we will utilize the 1-week placebo lead-in period to stratify by baseline ADHD symptom severity, >35 or ≤35, prior to randomization and not randomize those who report no marijuana use during this lead-in period. In our prior cannabis trials we have used this procedure such that we did not randomize those who ceased using marijuana.

If a patient does experience any uncomfortable side effects, the dose will not be raised, and if necessary, the dose will be lowered. Patients will be encouraged to set a quit date three weeks after starting study medications (the end of the titration phase of MAS-XR). During week 12 patients on active medication will be tapered off MAS-XR.

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 12-week trial. The non-blinded pharmacist and the non-blinded clinical psychologist 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 12 week trial, or at the conclusion of the patient's involvement in the trial (if they do not complete all 12 weeks), patients will learn their treatment assignment.

Study medication will be over-capsulated with riboflavin to assess compliance using quantitative fluorometry. 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 twice a week will be examined for riboflavin. 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.

Patient Payments: 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). Patients will received $10 for travel expenses at each visit (2x/week). Weekly return of medication bottles will receive $10 each week.

Once entered into the study, patient can earn progressive weekly cash payments if they come to their study appointments, complete the required assessments, and provide a urine sample at each visit. Starting at $2.50 for the first study visit, the value of the cash incentive for each subsequent consecutive visit is doubled to a maximum of $25. Failure to attend study appointments, complete study assessments, and provide a urine sample will reset the value of cash incentives back to their initial $2.50 from which the value can escalate again according to the same schedule. If an individuals attends all visits, they could earn $563 in cash over a 12 week period. This reinforcement schedule occurs independently from the cash received for bottle return described above and cash compensation for travel.

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 weeks 4 and 8 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 5-7 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 twice 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
table 1 study design.pdf
medication titration schedule-table 2.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation
Study Discontinuation
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) participant developing serious psychiatric symptoms (ADHD) as indicated by a Clinical Global Impression (CGI) improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks
2) participant's continued cannabis **use disorder**, even if improved from baseline, places him/her at risk for self-destructive behavior or other harm as indicated by a CGI improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks
3) female participant becoming pregnant as assessed by monthly urine pregnancy testing will result in cessation of the medication component but the option of continued participation in the trial and behavior therapy component.

Acute THC dosing can produce rises in blood pressure and heart rate, whereas chronic use may produce cardiovascular tolerance and rebound elevations in blood pressure/heart rate during cannabis withdrawal.

Addition of amphetamine may increase these elevations further. Further, while we exclude individuals who have any history of a psychotic disorder or bipolar illness, it is possible that amphetamines, in addition to ongoing cannabis use, might elicit psychosis among individuals with underlying vulnerability. To address these safety concerns we will closely monitor patients throughout the trial for any evidence of cardiovascular problems or emerging psychosis and address this accordingly, as outlined in the DSMP. If we have any cardiovascular concerns based on our close weekly monitoring, we will consult with our cardiologist, Dr. Angelo Biviano. We have worked with him for close to a decade and he is well-acquainted with our outpatient clinical trials that test stimulant medications. Study medication discontinuation during the screening and study period will occur in the following instances:

1) If the patient develops signs of cardiovascular instability: weekly vital signs and clinical evaluation; pulse at rest > 100 or Blood Pressure at rest >140/90 mm Hg for more than 2 weeks or SBP>160, DBP>110, HR>110 sitting quietly after being at the clinic for a period of time will result in immediate discontinuation of study medications
2) Cardiac risks as defined as cardiovascular chest pain, fainting or arrhythmias.

If a participant needs to be discontinued from study participation, he or she will be given the opportunity to continue with therapy as provided in the study, and treated clinically by the study psychiatrist or referred to a more appropriate level of care as needed.

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, chem-7, glucose, complete blood count), urinalysis, 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 for THC with Creatinine will be conducted at each visit (2 per week) and serve as an objective marker of current cannabis use. Quantitative toxicology for amphetamine and methylphenidate will be conducted every visit beginning in week 2.

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, chem-7, glucose, complete blood count, urinalysis, and blood pregnancy test for women)(45 minutes). An ECG will be repeated at weeks 4 and 8 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, twice weekly 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
study assessments 4-11-16.pdf

Off label and investigational use of drugs/devices

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

Drug #1

Name of the drug
Extended-release mixed amphetamine salt

Manufacturer and other information

Other name: Adderall-XR®
Manufacturer: Shire and Teva

Approval Status
IND is approved
IND#
79322
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 12-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
Individuals do not have to participate in this study to receive treatment for their cannabis use disorder and ADHD. Stimulant medication therapies, such as methylphenidate (Ritalin) as well as certain psychotherapy methods, may be helpful in treating the symptoms of ADHD. Although there are no accepted pharmacotherapies for the treatment of CUD. Psychotherapeutic approaches are commonly used for encouraging reduction in use or abstinence of drugs of abuse in general. 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. 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
Potential Risks
There are several sources and types of risk. Physical risks are those associated with obtaining blood samples (which may leave bruises) and medication administration. Psychological and social risks include revelation of sensitive material. Legal risks, not associated with the study per se, are inherent in the behavior of illicit drug use. The primary source of study related risks in clinical trials of medications stem from the medication itself. The following summarizes relevant information from the FDA approved prescribing information for MAS-XR.
MAS-XR: Amphetamine analog effects, benefits, and risks are extremely well understood. We recently completed a study using MAS-XR for adults with cocaine use disorder and ADHD. In addition, there is an extensive literature using amphetamines for the treatment of child and adult ADHD. Moreover, there is a worldwide replacement literature for amphetamine dependence; the cumulative data indicate comparatively low risk and the potential for considerable benefit. Still, risks are clear and can occur singly as the result of the medication itself, from interactions, or from additive effects in patients who abuse marijuana while receiving a therapeutic regimen.

Risks of oral amphetamines include nervousness, insomnia, blood pressure increases or decreases, gastrointestinal distress, weight loss and several forms of dermatitis. Side effects can be reduced or eliminated by lowering or discontinuing the medication. More severe effects include possible cardiovascular toxicity, particularly arrhythmias, excessive blood pressure elevation and the behavioral consequences of excessive CNS stimulation particularly sleep disturbance. Paranoid delusions, hallucinations, aggressive behavior, panic, anxiety, and a period of post drug depression are possible. Stroke and convulsions, although possible, are extremely unlikely at the doses used and in the population studied. Serious risk will be minimized by careful screening and dosing. No severe adverse events have been noted in previous studies and the medication appears to be well tolerated. 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 over 4 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.

Participants may be at greater risk if they self-administer other drugs that interact with the study

medications. Participants in these studies are identified users of marijuana and possibly 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. In prior and ongoing studies that we are conducting with amphetamine analogs, no serious problems have emerged.
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.

Finally, potential legal risks for these participants who use illegal drugs are addressed. Participants are advised to keep private materials related to the study. A certificate of confidentiality will be obtained.

As one progresses through the treatment study, depressive symptoms may emerge as a result of participants using marijuana 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 any time. If participants become upset during the interviews/assessments, assistance will be made available to them.

Risks of Diversion The risks of stimulant diversion are small but not negligent. The SAMHSA National Survey on Drug Use and Health collects data on a broad array of substances of abuse, including non-medical use of prescription stimulants. For 2010, nonmedical stimulant use was 0.4%. While not insignificant, it is substantially lower than nonmedical use of tranquilizers or pain medication. The risk of abuse is of concern with the administration of amphetamine but is substantially lowered by administering extended release preparations. Nevertheless we will take several precautions to minimize the risks of abuse and/or diversion of MAS-XR. MAS-XR 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

The exclusion criteria 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, along with 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, chem-7, glucose, 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-XR 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.

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 (or psychiatrist) twice 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. Further, we will have participants come for a post-taper study visit approximately 7-10 days after the last dose of MAS-XR to ensure that they are not experiencing any untoward effects and collect final study measures. If we cannot get them to attend the clinic we will attempt to garner information over the phone.

A calibrated fluorometer will be used to test for riboflavin in the urine. For many years our group has been adding riboflavin to our medication capsules to assess for medication adherence. However, our group found that the visual determination of the presence/absence of riboflavin using UV lights was woefully inaccurate and could be improved by using a quantitative cut-off to determine the presence/absence of supplementary riboflavin (Herron et al. 2013). Thus we now have more accurate assessment for medication adherence.

Data and Safety Monitoring Plan

Patients are closely monitored throughout the trial as described above. Dr. Levin, 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. Maria Oquendo, Evaristo Akerele, 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. The SAEs and AEs will be reviewed by the DSMB on an annual and as-needed basis.

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 5-7 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 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
Confidentiality
A Certificate of Confidentiality will be acquired for this study from the National Institute on Drug Abuse to offer protection for the privacy of participants 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 participants 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 participants' 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 will apply for the Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
Benefits to participants include a comprehensive medical and psychiatric assessment, and possible improvement in their symptoms of CUD and ADHD.

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.

Study visits will occur twice a week. Patients will be reimbursed $10 for transportation at each study visit ($10/visit, with maximum of $240 over 12 weeks). In some instances when patients take alternative transportation (i.e. driving to the clinic) they will be reimbursed up to $20 in cash if they provide receipts for expenses such as tolls and parking. As described above, progressive cash incentives will be provided for study visit attendance and compliance with other study procedures. If a patient attended all visits during the 12 week study (which is highly unlikely), he/she could earn $563. This reinforcement schedule occurs independently from the cash received for bottle return (which is an extra bonus that can total a maximum of $120 over the 12 weeks) and compensation for travel ($10/visit, with maximum of $240 over 12 weeks).

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
CUD-ADHD cf unbolded 4-6-16.pdf
7280 IND-frl.pdf
Upload copy(ies) of bolded Consent Form(s)
Upload evidence of FDA IND approval(s)
Upload copy(ies) of the HIPAA form
PP2PDFPrepUEAuthorization 3-22-16.pdf
Upload any additional documents that may be related to this study
7280_FB_ProvApp_04-13-16.pdf

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Schedule of Study Assessments

Measure	**Screening**	**Lead-In**	**Double-Blind Trial Week**											
Study Week	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Post-taper visit**
MINI DSM psychiatric assessment	x													
Study Termination Form	Report					On						Occurrence		
Marijuana Use Assessments														
Time Line Follow SUD	x	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	**x**
Marijuana Withdrawal Checklist	x	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	**x**
Quantitative Toxicology for THC with Creatinine	x	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	**x**
CGI-O for Substance Use	x	x	x	x	x	x	x	x	x	x	x	x	x	**x**
Sleep assessment														**x**
Pittsburgh Sleep Quality Index	x				x				x				x	**x**
ADHD Assessments														
DIVA (Diagnostic Interview for ADHD in Adults)	x													
AISRS	x	x	x	x	x	x	x	x	x	x	x	x	x	**x**
CAARS-Self	x	x			x				x				x	**x**
CGI-O for ADHD Symptoms	x	x	x	x	x	x	x	x	x	x	x	x	x	**x**
Cognitive Assessment														
Barratt Impulsiveness	x													
Immediate and Delayed Memory	x						x							
GoStop	x						x							
Letter-Number Sequencing	*x*						*x*							
Delay Discount Program	x						x							
Other Psychiatric/Life Assessments														
Hamilton Depression. Scale	x	x			x				x				x	**x**
Quality of Life, Enjoyment, and Satisfaction	x						x						x	**x**
Medical Assessment														
Physical/Bloods	x												x	
Nursing Assessment	x	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
Serum HCG (Urine HCG except at baseline)	x				x				x				x	
Concomitant Meds Form	x	x	x	x	x	x	x	x	x	x	x	x	x	**x**
MDRU Adverse Event		x	x	x	x	x	x	x	x	x	x	x	x	**x**
Serious Adverse Event	Report					on						Occurrence		**x**
Medication Compliance		xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
12 Lead ECG	x				x				x				x	
HIV Testing	x													
Adherence Assessment														
Quantitative Toxicology for Amphetamine & Methylphenidate			**xx**	**xx**	**xx**	**xx**	**xx**	**xx**	**xx**	**xx**	**xx**	**xx**	**xx**	
Bottle Return with pill count	x	x	x	x	x	x	x	x	x	x	x	x	x	
Riboflavin Fluorometry	x	x	x	x	x	x	x	x	x	x	x	x	x	

Table 1. Overall study design

	Week 1	Weeks 2-3	Weeks 4-11	Week 12
	Single-Blind Placebo Lead-In	Induction Phase	Maintenance Phase	Taper Phase
Group 1	Placebo	MAS-XR (2 weeks)	MAS-XR 80 mg daily	MAS-XR taper
Group 2	Placebo	Placebo	Placebo	Placebo

Table 2. Medication Titration Schedule

Placebo Lead-In (Week 1)	Randomization (Day 1)	Week 2 Days 1-2	Week 2 Days 3-4	Week 2 Days 5-6	Week 3 Days 7-9	Week3 Days 10-12	Week 3 Day 13-14	Weeks 4-11	Week 12
Lead-In Phase	Induction Phase							Maintenance Phase	Taper Phase
Placebo qAM	MAS-XR	MAS-XR 20 mg/day	MAS-XR 30 mg/day	MAS-XR 40 mg/day	MAS-XR 50 mg/day	MAS-XR 60 mg/day	MAS-XR 70 mg/day	MAS-XR 80 mg/day	MAS-XR (taper)
Placebo qAM	**Placebo Group**	Placebo qAM.	Placebo qAM	Placebo qAM	Placebo qAM	Placebo qAM	Placebo qAM	Placebo qAM	Placebo q AM