Study: # 7343 entitled EFFECT OF CLONAZEPAM ON CANNABIS WITHDRAWAL AND RELAPSE IN TREATMENT-SEEKING PATIENTS: COMBINED INPATIENT/OUTPATIENT STUDY

PI: John Mariani, M.D.

NCT# NCT02913924

Study Protocol Date: 8/30/2016

New York State Psychiatric Institute

Institutional Review Board

August 30, 2016

To: Dr. John Mariani

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

Subject: Approval Notice

Your protocol # **7343** entitled: **EFFECT OF CLONAZEPAM ON CANNABIS WITHDRAWAL AND RELAPSE IN TREATMENT-SEEKING PATIENTS: COMBINED INPATIENT/OUTPATIENT STUDY** Protocol version date 08/30/2016 and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **August 30, 2016 to July 24, 2017.** (Reviewed at the Full Board meeting on July 25, 2016.)

Consent requirements:
☐ Not applicable:
☐ 45CFR46.116 (d) alteration of consent to obtain verbal consent for the telephone interview
√ Signature by the person(s) obtaining consent is required to document the consent process
☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

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

Field Monitoring Requirements: √ Routine ☐Special: _____

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

Cc: RFMH Business Office (NIDA U54DA037842-01; subcontract to CU); CUMC IRB

Encl: CF, HIPAA

EN/LG/alw4scr

Signed copy on file at IRB

Protocol Title:
Effect of Clonazepam on Cannabis Withdrawal and Relapse in Treatment-Seeking Patients: Combined inpatient/outpatient study

Version Date:
08/30/2016

Protocol Number:
7343

Clinic:
Substance Treatment And Research Services (STARS)

First Approval:
08/30/2016

Expiration Date:
07/24/2017

Contact Principal Investigator:
John Mariani, MD
Email: mariani@nyspi.columbia.edu
Telephone: 646-774-6140

Co-Investigator(s):
Margaret Haney, PHD

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
✓ Use of Investigational 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?
No
Who is the PI of the grant/contract?
Levin, Frances, MD
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

Lay Summary of Proposed Research
The proposed protocol is a double-blind, placebo-controlled **inpatient and outpatient study**, combining our inpatient model of cannabis withdrawal with our expertise in the clinical treatment of cannabis use disorder. We will enroll 80 patients seeking treatment for cannabis use disorder into **the inpatient phase** for 5 nights. After discharge from the inpatient phase, 12-weeks of outpatient treatment will be conducted. This **combined** design will provide a comprehensive understanding of clonazepam's effects on individuals with cannabis use disorder across a range of outcome measures while also testing the medication's ability to prevent relapse in cannabis-abstinent patients.

Background, Significance and Rationale

Background, Significance and Rationale
Cannabis use is increasing and numbers are likely to rise further with legalization (Hasin et al., 2015). Currently, approximately 24% of patients entering treatment for a substance use disorder have cannabis use disorder (CUD; SAMHSA, 2013), yet their outcome is poor (MTPRG, 2004; Budney et al., 2006; Kadden et al., 2007; Levin et al., 2011, 2015). There is a clear need for FDA-approved pharmacological options to improve cannabis treatment outcome.

The purpose of this study is to test the effects of the benzodiazepine, clonazepam, as a potential treatment for CUD. The rationale for testing a benzodiazepine is the following: Cannabis withdrawal is, in part, characterized by symptoms such as anxiety and disordered sleeping (Haney et al., 1999, 2005; Budney et al., 2004), and clonazepam is efficacious and used therapeutically to treat both of these symptoms. Although benzodiazepines have the potential for abuse, clonazepam has a long half-life and is less reinforcing that fast-onset benzodiazepines (alprazolam, lorazepam) so was selected to be a time-limited treatment to facilitate the transition from regular cannabis use to abstinence.

Nonetheless, clonazepam is a controlled substance, and its administration to patients with a substance use disorder requires careful monitoring and minimization of the potential risks for misuse and physiological dependence. During the inpatient study period, study medication will be distributed on a single dose basis. During the outpatient period, study medication (clonazepam vs. placebo), will be distributed at weekly intervals and pill counts and biological measures of medication compliance (e.g., quantitative riboflavin) will be performed. The overall time period of potential exposure to clonazepam will be 8 weeks, with a 4 week time medication-free observation period following taper and discontinuation of study medication. These study features should minimize the risk of exposing individuals with CUD to clonazepam.

In order to most fully characterize the effects of clonazepam in patients seeking treatment for CUD, we have developed a novel **inpatient and outpatient study, combining our inpatient human laboratory model of cannabis withdrawal with our expertise in the outpatient treatment of CUD**. We will enroll patients seeking treatment for CUD into our inpatient laboratory for 5 nights, where we will initiate medication administration and test the influence of clonazepam on (1) cannabis withdrawal (mood, sleep, cannabis craving, food intake), ratings associated with medication abuse liability, cognitive performance, and (2) relapse to cannabis use after patients (now abstinent from cannabis) leave the inpatient setting maintained on clonazepam (or placebo) for 8 weeks (with a 4-week, medication-free follow up). This **combined** design will provide a comprehensive understanding of clonazepam's effects on individuals with cannabis use disorder across a range of outcome measures (safety, abuse liability, withdrawal symptoms) while also testing the medication's ability to prevent relapse in cannabis-abstinent patients.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
Primary Outcome Measure:
(1) Cannabis withdrawal (mood, sleep quality and duration, food intake)
(2) Cannabis relapse defined as (1) time to any MJ use as recorded by the timeline follow back method and

confirmed by urine metabolite levels, or (2) time to dropout, whichever comes first, and (3) medication compliance (% of pills taken) or time to discontinuation. Participants who relapse will continue in the trial to obtain secondary outcome measures.

Secondary Outcome Measures:

(1) Abuse liability (medication liking, desire to take again)
(2) Cognitive task performance
(3) Side effects and tolerability.

Description of Subject Population

Sample #1

Specify subject population
Adults with CUD
Number of completers required to accomplish study aims
60
Projected number of subjects who will be enrolled to obtain required number of completers
80
Age range of subject population
18-65

Gender, Racial and Ethnic Breakdown
Based on on-going research, it is expected that 20-30% of applicants will be female and 30% will have an ethnic identity of Hispanic. In terms of race, 30-40% are estimated to be Caucasian, 60-70% African American, and 5% Native American, Asian and Pacific Islanders, Eskimos, or Aleuts.
Description of subject population
We plan to enroll 80 participants into the study who meet criteria for current CUD and all other study criteria.

Recruitment Procedures

Describe settings where recruitment will occur
The project will be completed at the inpatient unit at NYSPI and 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 inperson 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 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 will be asked to come to STARS for additional screening as per protocol #6582R. Those patients who meet criteria for CUD 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 inperson 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
Create or insert table to describe the inclusion criteria and methods to ascertain them

1) Meets DSM 5 criteria for CUD of at least moderate severity (≥ 4 symptoms) and is seeking treatment for cannabis use.	Clinical interviews (telephone, psychologist, physician)
2) Reports using cannabis an average of 5 days per week over the past 4 weeks	Timeline Follow-back procedure modified for marijuana (MJ-TLFB); urinary THC-COOH > 100 ng/mL
3) 18-65 years of age	Legal identification

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

1) Individuals with a lifetime DSM-5 diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder	MINI International Neuropsychiatric Interview for DSM V and psychiatric assessment
2) Individuals meeting current DSM-5 criteria for any other psychiatric disorder that may, according to the investigator's judgment, require either pharmacological or non-pharmacological intervention over the course of the study	MINI International Neuropsychiatric Interview for DSM V and psychiatric assessment
3) Participants taking psychotropic medication	Psychiatric assessment
4) Known history of allergy, intolerance or hypersensitivity to benzodiazepines	Psychiatric assessment, medical history, physical examination, and serum and urine laboratory testing
5) Episodic or chronic use of benzodiazepines	MINI International Neuropsychiatric Interview for DSM 5 and psychiatric assessment, urine toxicology; urine toxicology
6) Pregnancy, lactation, or failure to use adequate contraceptive methods (condoms, diaphragm, birth control pill, IUD) in female patients who are currently engaging in sexual activity with men.	Clinical interview, Medical history, and serum HCG
7) Unstable medical conditions, such as poorly controlled hypertension, which might make participation hazardous	Medical history, physical examination, electrocardiogram, and serum and urine laboratory testing
8) Participants with a current DSM-5 diagnosis of an alcohol of substance use disorder (abuse or dependence) other than cannabis or nicotine use disorder	MINI International Neuropsychiatric Interview for DSM 5 and psychiatric assessment, urine toxicology,

	breathlyzer
9) Are legally mandated to participate in a substance use disorder treatment program	MINI International Neuropsychiatric Interview for DSM 5 and psychiatric assessment
10) Increased risk for suicide	MINI International Neuropsychiatric Interview for DSM 5 and psychiatric assessment
11) Current parole or probation	Self-report during interview
12) Recent history of significant violent behavior	Clinical interview
13) History of current of past diagnosis of glaucoma	Medical history, physical exam
14) History of benzodiazepine or other sedative hypnotic use disorder	**MINI International Neuropsychiatric Interview for DSM 5 and psychiatric assessment**

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 inperson 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
Naqvi, Nasir, MD
Shulman, Matisyahu
Vaezazizi, Leila
Williams, Arthur
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Study Participants: Participants will be 80 men and nonpregnant women with CUD who report using cannabis a minimum of 5 days per week over the past 28 days. The minimum threshold of a near-daily pattern of cannabis use will select a population with moderate-to-severe CUD. This level of severity is consistent with the sample in our previous clinical trial (Levin et al. 2011), and, we suspect, typical of individuals with CUD who seek treatment. This sample is less likely to achieve abstinence spontaneously or in response to non-medication aspects of the trial (e.g., general therapeutic support), and thereby minimize the placebo response rate. Selecting for near-daily cannabis users will also prevent a “floor effect” (i.e., participants using cannabis infrequently at baseline would be unlikely to demonstrate significant improvement).

Inpatient phase: Patients seeking cannabis treatment will move into the inpatient unit at NYSPI for 5 nights. On move-in day, participants will only receive the PM capsule administration; all capsules will be given under observation and will be double blind. During the next 4 days (days 2-5; Table 1), we will measure medication effects on cannabis withdrawal, including measures of mood, cannabis craving,

objective and subjective measures of sleep, and food intake in our Outpatient Marijuana Laboratory. Cannabis relapse measures will begin following discharge on day 6.
Outpatient phase: After discharge from the inpatient phase, 12-weeks of outpatient treatment will be conducted (Table 2). Study visits will occur twice weekly. One visit per week will be with the research psychiatrist for a Medical Management session to perform study assessments and to monitor medication effects and compliance. 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 cannabis and other substances, and encourages mutual-support group attendance. The second visit each week will be for vital sign monitoring, urine toxicology and completion of self-report measures. Participants will be given cash incentives contingent on study visit attendance and completing other study procedures with the objective of achieving a high treatment adherence.

We will emphasize at each visit the importance of not stopping medication use abruptly. If participants wish to stop or use less medication at any point, we will initiate a taper with them. This outcome will be part of our secondary endpoint (medication adherence and tolerability).

Medication: Clonazepam and matching placebo will be prepared by our pharmacy at the NYSPI, packaged in matching gelatin capsules with lactose filler in each capsule. The research pharmacist, who has no contact with patients, is the only non-blind member of the research team. At each weekly visit the psychiatrist orders the dose of double-blind medication for the coming week according to the schedule (Table 2). The psychiatrist will adjust the dose according to tolerability. Clonazepam or matching placebo will be given in a fixed-flexible dose schedule with clonazepam dose titrated to 2mg per day or the maximum tolerated dose.

Clonazepam or matching placebo will be taken twice per day in the morning and in the evening. The medication will be packaged in gelatin capsules with lactose filler plus 12.5mg of riboflavin. Clonazepam or matching placebo are given in a "fixed flexible" dose schedule with the dose titrated to 2mg per day or the maximum tolerated dose.

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 0.5mg/day of clonazepam, the medication will be discontinued.

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 patient who miss their scheduled appointments to remain on stable medication.

Medication Taper: During week 8, study medication will be tapered gradually to off (see table 2). This gradual discontinuation of study medication will minimize the discontinuation effects for participants exposed to clonazepam over the prior 7-week study period. For individuals exposed to clonazepam (a BZD with a long half-life) for a seven week period, a one week taper of study medication will be adequate to avoid the risk of physiological withdrawal. Participants will be monitored for the development of BZD withdrawal during and after the taper period, and will be managed clinically if significant withdrawal

symptoms emerge. It is unlikely that the length of time participants are exposed to clonazepam during the protocol will result in the development of physiological dependence that makes discontinuation difficult. However, there may be cases where participants due experience difficulty with the length of the taper schedule. If clinically significant withdrawal symptoms emerge during the taper, the taper may be extended for a second week based on clinical judgment by the study psychiatrist.

We will evaluate the adequacy of the double-blind by asking patients which treatment drug they think they are receiving. The blinded nurse will also be asked to report which drug s/he thinks each patient is taking. The research staff that administers medication 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 will be the only ones who have access to this information during the trial. However, a sealed envelope will be kept in the 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), patient 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 twice per week will be examined for riboflavin. In addition, folic acid in the form of a 1mg "pill" will be added to all placebo capsules in an attempt to improve the blind. The patient will receive up to 2mg of folic acid daily. Patients will receive medication in non-childproof packaging.

Medication Adherence Enhancement: We will use a combination of the quantitative fluorometric riboflavin determination method developed by our research group (Herron et al. 2013), timeline followback interview, and pill count with a weekly financial incentive ($10) for medication bottle return to both enhance and measure medication adherence. Note, participants will be instructed to take their morning capsules and come to the clinic within 6-8 hours to ensure that riboflavin levels will be detectable.

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.

You can upload charts or diagrams if any
Table 1 inpatient.pdf
Table 2 outpatient med dosing.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Patient Monitoring and Removal from the Study during Outpatient Phase
The psychiatrist and/or therapist will assess appropriateness for continuation in the research study on a

continuous basis, and will remove from the trial patients with significant clinical deterioration or noncompliance of a type that could be dangerous. Criteria for removal from the study will include:

1. Development of serious psychiatric symptoms as indicated by a Clinical Global Impression (CGI) improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks.
2. If the participant's continued cannabis use places him or 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. Development of serious medical conditions that may or may not be related to study participation (e.g., vital sign measurements, and monthly serum and urine laboratory studies.)
4. If the participant becomes pregnant as assessed by monthly urine pregnancy testing.

In case that the patient is removed from the research trial for medical reasons, or is requesting withdrawal from the study, he/she will be retained in open treatment for the remaining of the study period. Upon removal of a patient from the trial due to clinical deterioration, the patient will be referred for appropriate follow-up treatment, in most instances either intensive outpatient or residential treatment. The PI or a study psychiatrist is available 24 hours/day by phone and/or beeper in case of emergency.

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, weeks 4, 8, 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. Approximately, 80 ml of blood will be drawn overall (i.e., baseline, weeks 4, 8, and study completion = 4 x 20 ml =80 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.

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

Ongoing Psychiatric and Medical Assessments: The research psychiatrist will conduct weekly assessments of the psychiatric and medical status of the study participants. Participants taking psychotropic medications will be excluded. Participants who meet criteria for clinical worsening (e.g., CGI improvement >5 two weeks in a row) or the development of unacceptable medical or psychiatric risks will be removed from the trial and referred for appropriate treatment.

Outpatient Study Assessments

Adverse Effects measures: The Systematic Assessment for Treatment and Emergent Events (SAFTEE; Johnson et al. 2005) adapted for clonazepam will be performed weekly to identify adverse symptoms.

Benzodiazepine withdrawal measure: The Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B)(Busto, 1989) is a 22-item scale to assess the degree of benzodiazepine withdrawal.

Cannabis Craving measure: The Marijuana Craving Questionnaire (MCQ) is a 47-item instrument (Heishman et al. 2001).

Columbia Suicide Severity Rating Scale: Will be used to monitor suicidality at baseline and twice a month during the study period.

Medical Evaluation and Monitoring: A medical history and physical exam will be performed during screening. Serum pregnancy testing will be performed during screening and urine pregnancy testing will be performed monthly during the study. Complete blood count, electrolyte, urinalysis and liver function tests will be performed during screening and monthly during the study. Height and weight will be measured and baseline body mass index (BMI) calculated during screening. Temperature, pulse, blood pressure, and weight will be measured at every study visit.

Cannabis Use Outcome measures: Cannabis use will be recorded by the timeline followback (TLFB) method (Litten and Allen 1992) modified for cannabis and confirmed by creatinine-normalized quantitative urine THC levels. Other substance (including nicotine and alcohol) use self-report data will also be gathered during the TLFB interview. Urine samples for quantitative urine THC levels and creatinine will be collected under directly-observed conditions during screening and at each study visit (twice weekly). Creatinine levels can be used to control for urine concentration variability and screen for adulterated samples. Creatinine-corrected quantitative urine THC levels will then be used to confirm self-reported cannabis use, using a method similar to that described by Preston et al. (Preston et al. 1997) for cocaine dependence, where an obvious pattern of new use (i.e., level more than doubles in the past two days) overrides a self-report of no use.

Cannabis Withdrawal measure: We will use the 22-item version of the Marijuana Withdrawal Checklist (MWC; Budney et al. 1999) that measures subject-rated severity as the primary outcome measure of withdrawal.

Clinical Status: The Clinical Global Impression Scale-Observer (CGI; Guy 1976) will be used to measure the overall clinical status of the participant as well change from baseline in symptom severity. The Clinical Global Impression-Self (CGI-S) is a two-item scale that asks the subject to rate his or her current level of symptoms and estimate changes from baseline (Guy 1976).

Cognitive, Behavioral and Impulsivity Measures: A series of cognitive and behavioral measures will be performed at baseline, end of active medication treatment (week 8), and end of the observation period (week 12), to explore potential therapeutic mechanisms of action of the medication treatment.

Concurrent Treatment measure: The Modified Treatment Services Review assesses the past-week exposure to health care, psychiatric, or substance use disorder treatment (McLellan et al. 1992).

Medication Adherence measures: The Structured Pill Count Interview is a timeline followback assessment of study medication compliance accounting for each dose of prescribed study medication. Fluorometric detection of a urinary riboflavin concentration (Herron et al. 2013) will be used as a biological method to determine compliance with study medication.
Anxiety measure: A structured-interview version of the Hamilton Anxiety Scale (HAM-A; Hamilton 1959) will be used to assess mood and anxiety symptoms at baseline and changes associated with treatment.
Psychiatric Evaluation and Diagnosis: The MINI International Neuropsychiatric Interview will be performed during screening as part of a complete psychiatric diagnostic assessment.
Sleep measure: The Pittsburgh Sleep Quality Index Scale (PSQI; Buysse 1989) will be the primary outcome of sleep quality and length.

Please attach copies, unless standard instruments are used
outpatient study assessments 5-24-16.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
clonazepam
Manufacturer and other information

Other name: Klonopin, Klonopin Wafer
Manufacturer: Roche, Accord Healthcare, Actavis Elizabeth, Mylan, Sandoz, Sun Pharm Inds Inc, Teva, Vintage Pharms, Watson Labs

Approval Status
No IND is required
Choose one of the following options
FDA has determined that IND is not required

Off label and investigational use of devices

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 initiating the treatment program, during week 1 of the outpatient phase.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 3-4 weeks after their initial screening evaluation for the study. Medical management therapy will start during week 1 of the outpatient phase.
Treatment to be provided at the end of the study
At the conclusion of the 12-week outpatient 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. 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 risks associated with benzodiazepine misuse, withdrawal and overdose. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Misuse or taking benzodiazepines for long periods of time may lead to a drug habit, where a patient could become dependent on a benzodiazepine, such as clonazepam, to function. **Benzodiazepines are commonly misused and have a potential for abuse. They can have harmful effects and are easily available. Death and serious illness rarely result from benzodiazepines, such as clonazepam; however this medication can be dangerous when taken with either alcohol or other medications. The combination of substances can even cause death.** The most common adverse reactions noted with clonazepam are: drowsiness, confusion, dizziness, difficulty concentrating and loss of memory. Participants will be cautioned against driving a car or operating machinery, and will be warned against stopping the medication abruptly or drinking alcohol while participating in the study. We will also closely monitor for abuse-related behavior, both in our rating scales and in our weekly clinical visits.

An additional of risk of research participation is cannabis withdrawal, e.g., irritability, anxiety, disruptions in sleep and/or food intake. All participants are fully informed of the side effects that they might experience, and because all currently smoke cannabis, these effects should be familiar to them. Finally, the combination of clonazepam and cannabis may have additive intoxicating effects. **The research psychiatrist will discuss misuse, withdrawal, and risks of overdose with each participant.**

Evaluation of whether the risk of treatment with the medication is considered acceptable for women of childbearing potential will be determined by the research psychiatrist. There is a known teratogenic potential of clonazepam in pregnant women. **It is not considered safe during pregnancy or breast-feeding.** Therefore, female participants who are currently engaging in sexual activity with males must use adequate methods of contraception (e.g., barrier or hormonal contraceptive devices). Serum pregnancy tests will be conducted during screening and urine pregnancy tests will be performed monthly. If a female patient becomes pregnant and wishes to continue the pregnancy, she will be withdrawn from study medication and offered continuing non-pharmacological treatment (i.e., psychotherapy). **The research psychiatrist will discuss with the participant the risks, importance of adequate birth control practice, and will evaluate whether the participant is willing and reliable to practice effective birth control during the study. If a female participant becomes pregnant, they will be withdrawn from the study medication and the pregnancy will be followed to its outcome. Participants will be offered psychotherapy treatment with STARS or given referrals to other treatment centers until the conclusion of treatment.**

The structured interviews, rating scales, and questionnaires should add no physical risk. However, because many of the interviews and assessments are time-consuming to complete and involve topics of a sensitive nature, some people have found them to be physically or emotionally tiring. Patients are informed prior to study entry that they can refuse to answer any questions and that they can request to stop at any time. If a participant becomes agitated during any of the interviews or assessments, he or she will be provided with therapeutic assistance.

Inpatient Research Designs: There are minor risks of isolation, boredom, and inactivity associated with inpatient laboratory stays. In participants we have tested to date under similar conditions, such problems have been minimal. We describe at length possible difficulties of living in the lab before volunteers sign the

study consent form.
Phlebotomy: Participants will provide a blood sample during screening; they will be warned that blood drawing may cause slight discomfort at the site of needle entry and may result in a small bruise.

Describe procedures for minimizing risks

Participants are carefully screened for psychiatric risk prior to admission, so we anticipate the risk of clinically-significant psychological deterioration during participation to be low. However, participants will be removed from the study and assessed by a member of the clinical staff if, at any stage during participation, they: 1) experience a panic attack, as diagnosed by DSM-5 criteria; 2) experience significant psychological deterioration as indicated by self-reported anxiety or depressed mood producing clinically significant distress beyond the discomfort typically experienced during cannabis withdrawal; 3) report the development of suicidal ideation; or 4) show functional deterioration as indicated by inability to comply with study procedures or erratic or aggressive behavior. After a patient is removed from the protocol, clinical staff will undertake a risk assessment and determine the appropriate course of action, including but not limited to admittance to the emergency department of New York Presbyterian, and referral for outpatient treatment.

Recruitment and Informed Consent: Participants will be recruited via various media advertisements. The first phase of recruitment is a structured telephone interview. Those volunteers passing the initial interview visit the laboratory and receive a brief description of the study and are asked to consent to be screened. This screening consent form covers all interviews, questionnaires, and collection of appropriate medical information. They receive a physical exam (including blood and urine tests), ECG, medical history evaluation, and psychiatric interview. Only those judged psychiatrically and physically healthy are accepted to continue. As a part of this first tier of screening, volunteers are also shown the laboratory. They are given the opportunity to ask questions and discuss participation at length. Only after that has been accomplished are participants started in the protocol.
Protection Against Risk: Our procedures and monitoring are designed to minimize study risks. Behavioral observations are made throughout laboratory sessions and the subjective reports of participants are carefully considered. A physician will be on call in the event of an emergency. Emergency medical equipment is available in our laboratory. In the clinic, physicians are on site at all times and the NYC 911 system can be activated in case of a medical emergency. We anticipate, however, that careful participant selection, dose selection and participant monitoring will obviate the need for such care. Participants are free to leave the study at any time and care is taken to be sure that this is understood. They are fully informed of the potential side effects of cannabis and clonazepam. Our research group has been conducting inpatient and outpatient clinical pharmacology research for more than 20 years and our careful precautionary measures should ensure that no serious adverse incidents occur.
Confidentiality: We deal with issues of confidentiality by using coded records, storing signed consent forms in a locked safe, and trying to the best of our ability to maintain confidentiality. We obtain certificates of confidentiality for all of our research protocols.

<u>Data and Safety Monitoring Plan</u>
Every six months, the PI, the Co-Investigators, Data Manager will review the number of patients enrolled, the number who completed the protocol, the number who dropped out of the protocol prior to completion

(and reason why), any adverse events, procedures for assuring patient privacy and confidentiality, and the quality and integrity of the data collected. Corrective action will be taken if needed. IRB protocols and informed consent documents will be reviewed annually by the IRB. Reports of enrollment and retention and reporting of adverse events are required with these renewals. In addition, all studies involving human subjects are periodically and systematically reviewed by the New York State Quality Assurance Staff for the New York site. These procedures assure protocol compliance by conducting unannounced reviews of participants' research charts, comparing research charts to the IRB protocol.

In addition, a separate Data Safety and Monitoring Board (DSMB) will meet yearly with the Internal Advisory Board of the Center and the PIs of the Project to review study admission data, protocol compliance, safety data (review of adverse events and serious adverse events), and efficacy data for all studies. The DSMB members are Drs. Maria Oquendo, Soteri Polydorou, and Evaristo Akerele. After each meeting of the DSMB, the executive secretary will forward a summary report of all serious and unexpected adverse experiences to each investigator. The report will summarize the Board's review of cumulative serious and unexpected adverse events reported without specific disclosure by treatment arm. Furthermore, the report will inform investigators of the Board's recommendations with respect to progress or need for modification of the protocol.

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 marijuana, cocaine, other street drugs, or alcohol. Patients will give informed consent before entering the study. 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

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
Participants will receive up to an additional four weeks of free treatment for CUD following the end of the study period. In addition to the experimental treatment of clonazepam, all participants will receive Medical Management, a supportive behavioral treatment of established efficacy.

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.

Subject Compensation: Patients will be provided $50/night for their inpatient phase ($250 for 5 nights); they will also receive $10 for travel at each study visit and will receive an additional $10 each week for returning their medication bottle with any remaining pills. These payments are in addition to progressive cash incentives for study visit attendance (maximum: $512.50).

Study Visits and Cash Incentives for Attendance: Progressive cash incentives will be provided for study visit attendance and compliance with other study procedures. Starting at $2.50 for the first study visit, the value of cash incentives 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 individual attends all visits, they could earn $512.50 in cash. This reinforcement schedule occurs independently from the cash incentives received for bottle return and compensation for travel.

The maximum amount over the 12 weeks you may potentially earn for attending all study visits is $1072.50. Participants can potentially earn $250 for the inpatient phase, $512.50 in weekly cash payments, $230 in cash for transportation costs, and $80 in cash for pill bottle returns.

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
CUD-clonaz cf unbolded 8-9-16.pdf
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of the HIPAA form

PP2PDFPrepUEAuthorization 7-5-16.pdf
Upload any additional documents that may be related to this study
7343_FB_prov_app_memo_08-11-16.pdf
IND -- 7343.pdf

References

References
1. Budney AJ, Moore BA, Rocha HL, Higgins ST (2006) Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. J Consult Clin Psychol 74(2): 307–316.
2. Busto, U.E., Sykora, K. and Sellers, E.M. (1989). "A clinical scale to assess benzodiazepine withdrawal." Journal of Clinical Psychopharmacology 9(6): 412-416.
3. Cannabis Treatment Project Research Group (2004) Brief treatments for cannabis dependence: Findings from a randomized multisite trial. J Consult Clin Psychol 72(3): 455–466.
4. Cerdá M, Wall M, Keyes KM, Galea S, Hasin D (2012) Medical cannabis laws in 50 states: Investigating the relationship between state legalization of medical cannabis and cannabis use, abuse and dependence. Drug Alcohol Depend 120(1-3): 22-27.
5. Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Foltin RW (2008) Effects of THC and lofexidine in a human laboratory model of cannabis withdrawal and relapse. Psychopharmacology (Berl) 197(1): 157-168.
6. Hasin DS, Saha TD, Kerridge BT, Goldstein RB, Chou SP, Zhang H, Jung J, Pickering RP, Ruan WJ, Smith SM, Huang B, Grant BF (2015) JAMA Psychiatry, in press.
7. Kadden RM, Litt MD, Kabela-Cormier E, Petry NM (2007) Abstinence rates following behavioral treatments for cannabis dependence. Addict Behav 32(6): 1220–1236.
8. Levin FR, Mariani JJ, Brooks DJ, Cheng W, Nunes EV (2011) Dronabinol for the treatment of cannabis dependence: A randomized, double-blind, placebo-controlled trial. Drug Alcohol Depend 116(1-3): 142-150.
9. Levin FR, Mariani JJ, Pavlicova M, Brooks DJ, Glass A, Mahony A, Nunes EV, Bisaga A, Dakwar E, Carpenter KM, Sullivan MA, Choic JC (2015) Dronabinol and lofexidine for cannabis use disorder: A randomized, double-blind, placebo-controlled trial. Drug Alcohol Depend, in press.
10. Substance Abuse and Mental Health Services Administration (SAMHSA) (2013) Results from the 2012 National Survey on Drug Use and Health: Summary of national findings.
11. Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality (2012) The TEDS report: Cannabis admissions reporting daily
12. Brown, H., & Prescott, R. (1999). Applied Mixed Models in Medicine. Chichester: John Wiley & Sons. use at treatment entry.
13. Little, R., & Rubin, D. (2002). Statistical Analysis with Missing Data. Hoboken, NJ: Wiley.
14. Diggle, P., & Kenward, M. G. (1994). Informative drop-out in longitudinal data analysis. Applied Statistics, 43(1), 49-93.
15. Diggle, P. J., Heagery, P., Liang, K. Y., & Zeger, S. L. (2002). Analysis of Longitudinal Data (2nd ed.). Oxford, UK: Oxford University Press.
16. Rotnitzky, A., Robins, J. M., & Scharfstein, D. O. (1998). Semiparametric regression for repeated outcomes with nonignorable nonresponse. Journal of the American Statistical Association, 93, 1321-1339.
17. Rotnitzky, A., Scharfstein, D., Su, T. L., & Robins, J. M. (2001). Methods for conducting sensitivity

analysis of trials with potentially nonignorable competing causes of censoring. Biometrics, 57, 103-113.
18. Scharfstein, D. O., Rotnitzky, A., & Robins, J. M. (1999). Adjusting for nonignorable drop-out using semiparametric nonresponse models. Journal of the American Statistical Association, 94, 1096-1146.
19. Kenward, M. (1998). Selection models for repeated measurements with non-random dropout: an illustration of sensitivity. Statistics in Medicine, 17(23), 2723-2732.

Table 3: Outpatient Study Assessments

	X once weekly; XX twice weekly	Screening	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Medical Evaluation	Medical History and Physical Examination	x													
	Pregnancy, serum	x													
	Pregnancy, urine		x				x				x				x
	Psychiatric Evaluation	x													
	Serum Laboratory Examination	x					x				x				x
	Urinalysis	x					x				x				x
	Urine Toxicology	x	x	X	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x
	Urine Fluorometry (quantitative riboflavin)			x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x
	Vital signs (weight, pulse, blood pressure, and temperature)	x	x	x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x
Interview	CIWA-BZD									X	X	X	X		
	Clinical Global Improvement Scale (CGI)-Observer		x	x	x	x	x	x	x	x	x	x	x	x	x
	C-SSRS	x	x		x		x		x		x		x		x
	Hamilton Anxiety Scale (HAM-A)		x		x		x		x		x		x		x
	MINI International Neuropsychiatric Interview	x													
	Structure Pill Count Interview			x	x	x	x	x	x	x	x	x	x	x	x
	Systematic Assessment for Treatment and Emergent Events (SAFTEE)		x	x	x	x	x	x	x	x	x	x	x	x	x
	Timeline Follow-Back (TLFB)	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Treatment Services Review (TSR)		x	x	x	x	x	x	x	x	x	x	x	x	x
Self-Report	Clinical Global Impression (CGI)-Self		x	x	x	x	x	x	x	x	x	x	x	x	x
	Marijuana Craving Questionnaire (MCQ)		x	x	x	x	x	x	x	x	x	x	x	x	x
	Marijuana Withdrawal Checklist (MWC)		x	x	x	x	x	x	x	x	x	x	x	x	x
	Pittsburgh Sleep Quality Index (PSQI)		x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1: Inpatient Phase Medication Dosing						
Day	**1**	**2**	**3**	**4**	**5**	**6**
Study Groups	**Move-in**	***Withdrawal, cognition, abuse liability***				**Move-out**
Clonazepam (mg/day)	1.0	2.0	2.0	2.0	2.0	2.0
Placebo (mg/day)	0.0	0.0	0.0	0.0	0.0	0.0

Table 2. Outpatient Phase Medication Dosing

Study Groups	Week 1 Days 6-7 (outpatient)	Weeks 2-7 Days 8-49 (outpatient)	Week 8 Days 50-51 (outpatient taper)	Week 8 Days 52-54 (outpatient taper)	Week 8 Days 55-56 (outpatient taper)	Week 9-12 Days 57-84 (outpatient obervations)
Experimental Group	clonazepam capsules 1 mg twice daily	Clonazeapam capsules 1 mg twice daily	Clonazepam capsules 0.5 mg QAM and 1 mg QHS	Clonazepam capsules 0.5 mg QAM and 0.5 mg QHS	Clonazepam capsules 0.5 mg QHS	No study medication
Placebo Group	Placebo capsules Twice daily	Placebo capsules twice daily	Placebo capsules twice daily	Placebo capsules twice daily	Placebo capsule QHS	No study medication