Study: # 7977 entitled Pregabalin Trial for the Treatment of Alcohol Use Disorder (GABI2)

PI: John Mariani, M.D.

NCT#: NCT04322305

Study Protocol Date: April 27, 2020

NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

April 27, 2020

TO: Dr. John J. Mariani

FROM: Dr. Edward Nunes, Co-Chair, IRB
Dr. Agnes Whitaker, Co-Chair, IRB

SUBJECT: **APPROVAL NOTICE*****

Your protocol # **7977** entitled **A Double-Blind, Placebo Controlled Trial Of Pregabalin For The Treatment Of Alcohol Use Disorder** (version date 04-27-2020) and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **April 27, 2020 to April 19, 2021.** (Reviewed by the Full Board on 04-20-2020.)

Consent requirements:

☐ Not Applicable:

√ 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 and stamped 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 be 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 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.**

******* Please note, only remote procedures may be conducted at this time. All in-person procedures are on hold until further notice, due to COVID-19 guidance. Please contact your Division Chief to discuss your specific protocol plan and contact the IRB prior to commencing any in-person procedures.***

CC: RFMH Business Office (R21AA028371)

ENC: CF (v. 04-23-2020); HIPAA form

EN/AHW/Scr

Signed copy on file at IRB

Protocol Title:
A Double-Blind, Placebo Controlled Trial of Pregabalin for the Treatment of Alcohol Use Disorder

Version Date:
04/27/2020

Protocol Number:
7977

First Approval:
04/27/2020

Clinic:
Substance Treatment And Research Services (STARS)

Expiration Date:
04/19/2021

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

Co-Investigator(s):
Frances Levin, MD

Research Chief:
Frances Levin, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting a new protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
Substance Use Disorders
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.

none

Procedures

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

✓ Psychiatric Assessment
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ Use of Investigational Drug or Device
✓ Off-label Use of Drug or Device

Population

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

✓ Medically and Psychiatrically Healthy Subjects
✓ Adults
✓ Adults over 50

Research Support/Funding

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

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract application is a pending review or a funding decision
Source of Funding
Federal
Institute/Agency
NIAAA
Grant Name
A Double-Blind, Placebo Controlled Trial of Pregabalin for the Treatment of Alcohol Use Disorder
Grant Number

R21AA028371
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Study Location

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

Lay Summary of Proposed Research

Lay Summary of Proposed Research
The proposed study is an 10-week double-blind, randomized controlled clinical trial comparing the efficacy of pregabalin to placebo in reducing harmful alcohol consumption. Fifty treatment-seeking participants will be actively drinking at study entry and randomized to treatment with pregabalin in dosages up to 600 mg or placebo, with the hypothesis that pregabalin will be tolerable, safe, and effective in reducing harmful drinking in outpatients who present for treatment actively drinking, but do not require an inpatient detoxification.

Background, Significance and Rationale

Background, Significance and Rationale
Alcohol use disorder continues to be a significant public health problem in the United States, despite considerable advances in the development of pharmacological and behavioral interventions, and substantial gaps in the treatment armamentarium remain. Conceptually, the ideal pharmacotherapy for alcohol dependence would: 1) be safe when administered to actively drinking patients; 2) provide protection against mild-to-moderate alcohol withdrawal; 3) promote reductions in harmful alcohol consumption; 4) reduce craving and relapse risk in abstinent patients; and 5) have a low potential for misuse. No current

pharmacotherapy for alcohol dependence meets all these criteria. Despite the availability of existing evidence-based alcohol use disorder pharmacotherapy (naltrexone, disulfiram, acamprosate, topiramate), the development of safe and effective pharmacotherapy for actively drinking outpatients with alcohol use disorder remains an important public health need.

Pregabalin is a gabapentinoid medication with preliminary evidence of efficacy in treating the symptoms of alcohol withdrawal and post-acute withdrawal symptoms, such as insomnia and anxiety, as well as evidence of efficacy as a relapse prevention agent. Like other gabapentinoids, pregabalin binds to subunits of voltage-gated calcium channels and inhibits calcium currents, resulting in a net effect of neuroinhibition. Pregabalin is estimated to be 2.5 times more potent than gabapentin, and there is pre-clinical and early clinical evidence for its use in the treatment of alcohol withdrawal symptoms, as well as reductions in harmful drinking. Pregabalin is a well-tolerated medication with a low abuse liability and minimal potential for drug-drug interactions, thereby making it ideal for use in the outpatient setting. Actively-drinking outpatients often have difficulty reducing harmful alcohol consumption because of symptoms of withdrawal, craving, anxiety, and insomnia that can accompany reducing or stopping alcohol use. Pregabalin has well matched clinical effects of anxiolysis, sedation, reduction of craving and alcohol withdrawal symptoms. If proven to be efficacious in facilitating reduction in harmful alcohol consumption, pregabalin, with its favorable safety and tolerability profile, could broaden the range of treatment options for alcohol use disorder outpatients as well as potentially enhance treatment outcomes. We conducted an eight-week open-label pilot study testing the safety, tolerability, ideal dosing and feasibility of pregabalin for treatment-seeking alcohol use disorder patients with four or more heavy drinking days (HDD) per week at study entry. For the 15 participants with post-enrollment data, one-third (n=5) had no HDD in the final week of their study participation. For other alcohol use disorder outcomes (percent days abstinent, percent HDD, drinks per drinking day, drinks per week), measured from baseline to last week of study participation, there were significant improvements in all measures. In general, the medication was well-tolerated and there were no serious adverse events. The most common side effect was drowsiness (26.7%, 4/15), and fogginess, dizziness, and insomnia (all 20%, 3/15).

Specific Aims and Hypotheses

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Aim 1: To determine preliminary effect of pregabalin when compared to placebo for reducing harmful alcohol consumption in actively drinking outpatients with alcohol use disorder at the end of the study.

Primary Hypothesis: Pregabalin treatment will reduce harmful alcohol consumption at the end of the study as compared to placebo. The primary outcome measure will be the proportion of the heavy drinking days (defined as any day where the number of standard drinks was at least 5 for men and at least 4 for women) per week as measured by the timeline follow-back method. Change in HDD is a clinically relevant outcome measure that has been employed in AUD pharmacotherapy trials enrolling actively drinking participants (Johnson et al. 2007). The concept is that actively-drinking treatment-seeking participants (least 4 HDD/week at study entry) will demonstrate a greater reduction in HDD in the pregabalin group as compared to placebo.
Secondary Hypotheses: Pregabalin treatment of alcohol use disorder will improve other measures of alcohol consumption (percent participants abstinent, percent days abstinent, drinks per week, drinks per drinking day) at the end of the study as compared to placebo.

Exploratory Hypotheses: We will examine possible moderators and mediators, including alcohol withdrawal, anxiety, craving, and sleep measures, to explore causal mechanisms.

Description of Subject Population

Sample #1

Specify subject population
Adults with AUD
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 enroll 50 participants into the study. Both males and females will be recruited. All eligible subjects are accepted; however, past experience with recruitment for other studies in this population, it is estimated that the sample will be 75% male, 60% Caucasian, 30% Hispanic or Latino, and 10% Black or African-American.
Description of subject population
We plan to enroll 50 participants into the study who meet criteria for current AUD.

Recruitment Procedures

Describe settings where recruitment will occur
The project will be completed at the Substance Treatment and Research Services (STARS downtown) situated on 3 Columbus Circle, 14th Floor, Suite 1408, NY, NY 10019.
How and by whom will subjects be approached and/or recruited?
pastingScreening 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 AUD through newspapers, radio, internet, 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 AUD will be asked to come to STARS for additional screening as per protocol #6582R. Those patients who meet criteria for AUD 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 AUD
Create or insert table to describe the inclusion criteria and methods to ascertain them

a. Meets DSM-5 criteria for current alcohol use disorder	Clinical interviews; MINI
b. Reports drinking a minimum of 5 standard drinks for men or 4 standard drinks for women at least 4 days per week over the past 28 days	Self-report
c. Between the age of 18-65	Legal identification
d. Able to provide informed consent and comply with study procedures	Clinical assessment, MMSE (individuals over 60 years old)

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

a. Subjects with any current psychiatric disorder as defined by DSM-5, other than AUD, that in the investigator's judgment might require intervention over the course of the study, **including schizophrenia, schizoaffective disorder, psychotic disorders other than transient psychosis due to drug abuse, bipolar disorder, and current suicidality with plan and intent.**	Clinical interviews
b. Subjects receiving psychotropic medication treatment	Clinical interviews
c. Evidence of moderate-to-severe alcohol withdrawal (CIWA-Ar ≥10)	Self-report; CIWA
d. History of alcohol withdrawal seizures or alcohol withdrawal delirium	Clinical interviews
e. History of allergic reaction to candidate medication (pregabalin)	Self-report
f. Pregnancy, lactation, or failure in female patients to use adequate contraceptive methods	Serum pregnancy test, self-report
g. Unstable physical disorders which might make participation hazardous	Clinical assessment ; vital signs, laboratory tests, EKG
h. Subjects who have a current DSM-5 diagnosis of moderate or severe substance use disorder, with the exception of alcohol, nicotine and caffeine dependence. A diagnosis of a mild substance use disorder will not be exclusionary, as long as the current primary substance use disorder is alcohol dependence	Clinical interviews
i. Are legally mandated to participate in alcohol use disorder treatment program	Self-report

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)

No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
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
Blevins, Derek
Brezing, Christina, MD
Castillo, Felipe
Iqbal, Muhammad
Kidd, Jeremy
Levin, Frances, MD
Luo, Sean, MD
Mariani, John, MD
Naqvi, Nasir, MD
Shulman, Matisyahu, MD
Srivastava, A Benjamin
Wai, Jonathan, MD

Williams, Arthur
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Screening and Diagnosis: Uniform screening procedures will be used under protocol #6582R. A standardized telephone screen is followed by an appointment for those who meet general study criteria. No identifying information is recorded until the subject completes the study explanation and consent process; evaluation follows consent using standardized measures. Common, standardized intake and evaluation training will be conducted for all procedures and instruments. Points at which assessments will be made are listed in the assessments table. Data collected will be entered or uploaded and maintained in the clinical trials secure electronic database and coded with a unique identifier assigned to each participant. Hospital charts, and Departmental, HIPPA-compliant Research Subject Registration System (KISMER) will, however, contain participants' names. All screening and diagnostic assessments will be reviewed by the consenting research psychiatrist for study consent eligibility. Screening assessments include baseline assessments such as medical history, physical exam, EKG, laboratory results, psychiatric evaluation, MINI, and other assessment listed under protocol #6582R.

Medication and rationale: The rationale for studying pregabalin as a treatment for AUD using an abstinence initiation model is as follows: 1) the majority of patients seeking treatment for alcohol dependence are outpatients who are actively consuming alcohol and the proposed design would model this clinical presentation, 2) pregabalin has been shown to potentially be effective as treatment for alcohol withdrawal, 3) pregabalin has shown promise as a relapse prevention treatment. These characteristics suggest that pregabalin is a medication that potentially can be used to successfully transition individuals with AUD from active drinking to abstinence and reduce the risk of relapse.

Pregabalin will be administered in 75 mg and 100 capsules; placebo capsules will appear identical to the pregabalin capsules. Participants in both study arms will receive the same number of capsules. Pregabalin will be titrated over a 3-week period to the FDA maximum (600 mg per day) or the maximum tolerated dose. A dose of 300 mg daily, is clinically relevant for most FDA-approved indications. Labeling instructions for pregabalin, recommend for the initial titration, reaching a dose of 300 mg/day in no less than a week. We will follow those recommendations, and then continue to explore higher doses of pregabalin to determine the ideal dose, tolerability, and safety of pregabalin for AUD. In our pilot study, 12 of 15 individuals achieved and tolerated a dose of 600 mg daily. Dose reductions for tolerability will be made by the research psychiatrist in coordination with the research pharmacy. Medication will be dispensed in child-resistant bottles containing a one-week supply of medication.

The study will be run under the NYS Controlled Substance license # 0400081 held by the NYS OMH and the DEA Researcher Registration # PN0093461 held by the NYSPI Pharmacy Department. As soon as it is approved by NYS and the DEA, this project will be run under both the PI, Dr. Frances R. Levin's NYS Controlled Substance license (0401417) and her DEA Researcher Registration # RL0507941 and the NYS/OMH license and NYSPI DEA Researcher Registration.

The drug stock of controlled substances for each project will be ordered, maintained and prepared under the Institutional registration at the NYSPI Pharmacy (OMH/NYS Controlled Substance license # 0400081). Packaged drugs (kits) will be transferred to the Principal Investigator (Dr. Frances R. Levin) using a DEA 222 form with the address where the study will take place (e.g. 3 Columbus Circle, Suite 1408, NY, NY 10019). Drugs or kits for individual patients will be transferred from the Institutional registration (#0400081) to the investigator registration using DEA 222 forms and transported by Marcia Loughran, FNP (supervisor of controlled substance activity) to the 3 Columbus Circle Suite 1408, NY, NY 10019 research site. Drug will then be kept in the wall mounted, double-door, double-locked storage cabinets at 3 Columbus Circle until it is given to the participant.

Randomization: Participants will be randomly assigned to receive either medication or placebo. The randomization sequence will be balanced in blocks of random size (4, 6, 8) to prevent clinicians from guessing what the next patient's treatment might be. Additionally, the randomization will be stratified by gender and the severity of alcohol use (> 35 standard drinks/week). The purpose of the stratification is to distribute these potential confounding factors equally across treatment groups. To the extent that these stratification variables are predictive of outcome, stratifying by them should enhance statistical power to test treatment effects (Fleiss et al. 1986).

Study Visits: Participants will be asked to attend 5 study visits during week 1 (study days 1, 2, 3, 4, and 5 or 7). During the second week, study visits will continue every other day for a total of 3 study visits (study days 8, 10, and 12 or 14). During the remainder of the 8-week study period, study visits will occur twice weekly. There will be two visits during the post-study taper week. There will be final post-taper visit after study medication is discontinued. One visit per week will be with the research psychiatrist. Study assessments will be performed according to the schedule.

Medical Management Treatment: All participants will have a weekly supportive behavioral treatment session with the research psychiatrist using a manual designed for pharmacotherapy trials in subjects with alcohol use disorders (Pettinati et al. 2005).MM is used routinely in clinical trials at STARS. These 30-minute sessions will focus on psychoeducation and adherence to study medication, medical and psychiatric monitoring, including adverse events, encouraging the goal of abstinence, and discussion of other treatment goals.

Medication Adherence Enhancement: We will use a timeline followback interview and pill count with a weekly financial incentive ($10) for medication bottle return to both enhance and measure medication adherence. Our prior studies have found a 91% rate of bottle return using this method. Participants are not provided reinforcement for ingesting medication—payment is tied solely to the return of the medication bottle. We considered serum blood levels and riboflavin over-encapsulation and fluorometric quantification, but decided those interventions were not cost-effective given the limited budget of this exploratory investigation. Pregabalin is associated with some risk of misuse (Evoy et al. 2017), and to protect against this risk, medication will be dispensed in weekly bottles.

Ongoing Psychiatric and Medical Assessments: The research psychiatrist will conduct weekly assessments of the psychiatric and medical status of the study participants. Participants who meet criteria for clinical worsening (e.g., CGI improvement 6 (much worse than baseline) two weeks in a row) or the development of unacceptable medical or psychiatric risks will be evaluated for removed from the trial and

referred for appropriate treatment if deemed necessary.

You can upload charts or diagrams if any
medication dosing schedule.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation
Drop-out criteria during the screening and study period include:

1) Development of serious psychiatric symptoms as indicated by a CGI improvement score of 6 (much worse than baseline) or greater for two consecutive weeks*
2) Development of evidence of moderate-to-severe alcohol withdrawal (CIWA-Ar > 10) indicating a need for inpatient detoxification treatment
3) If the participant's continued alcohol use, 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*
4) If a female participant becomes pregnant
*Any occurrence of CGI score of 6 or 7 at any time will trigger a clinical evaluation and then clinical judgment as to whether the patient should be discontinued, rather than a definitive discontinuation criterion. Such evaluations will be documented in the clinical chart.

Referrals for treatment in the community will be provided for the appropriate level of care.

Participants may be removed from the trial if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment (drop out criteria are defined above). Participants who develop evidence of physiologic alcohol withdrawal will be dropped from the study or demonstrate a persistent clinically significant worsening of their alcohol use will be removed from the study and offered appropriate clinical referrals. Additionally, participants who develop serious psychiatric symptomatology (e.g., psychosis, suicidal ideation, severe depressive symptoms) during the study period will be dropped from the study and appropriate clinical referrals will be made. A patient whose continued alcohol use, even if improved from baseline, places him or her at risk for self-destructive behavior or any other significant harm will be discontinued from the study. This would include, but not be limited to, patients who engage in destructive or violent behavior while intoxicated, report blackouts, drive while intoxicated, or develop medical complications related to their alcohol use. In all cases where subjects are discontinued from the study, the clinical research staff will assume clinical responsibility for the subjects until such referrals are operational. History of allergic or adverse reactions to pregabalin is exclusionary.

Although a patient might potentially attempt to overdose with pregabalin, those individuals who are risk for suicidality will be excluded and those who are deemed to be at significant risk for suicide will be referred to a more intensive level of care. Subjects will be provided with at most a seven-day supply of medication at one time during the study.

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 for routine analyses including complete blood count, electrolytes, liver function tests, and blood pregnancy test for women. They may be repeated during the study if clinically indicated.

Urinalysis: Laboratory urinalysis will be performed during the screening process.

Urine Toxicology: Urine samples for toxicology will be collected under directly observed conditions during screening and study weeks 4 and 8 to detect any non-alcohol substance use.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Eligibility Determination via Physical Examination and Psychiatric Evaluation: Review of history, physical, and laboratory evaluations and the medical-psychiatric evaluation note lead to final determination of eligibility will be done by the study psychiatrist trained on the protocol.

The MINI International Neuropsychiatric Interview (MINI): will be performed during screening as part of a complete psychiatric diagnostic assessment. The research psychiatrist will assess all potential participants for DSM-5 psychiatric disorders. All new cases are presented at the weekly clinical research staff meeting attended by the PI (Dr. Mariani), co-investigator (Dr. Levin) other investigators and physicians, research nurses, treating therapists and consensus about diagnosis is reached. Diagnostically confusing cases will be interviewed by the PI.

Medical Screening and Evaluation: Medical examination and laboratory work will follow consent. ECGs, blood draws, and urinalyses will be obtained by a lab technician. All tests are conducted using accepted clinical techniques and samples (e.g. bloods) are collected using universal precautions. Pregnancy tests will be conducted for women. A Health Survey will be conducted with special attention devoted to cardiovascular function. A cardiologist is available for STARS participants and will review any abnormal ECGs, and determine whether or not a patient can be safely enrolled in the trial.

Physiological Measures:
Alcohol Breath Testing: Alcohol breath testing will be performed at every study visit.

Medical History and Physical Exam: A comprehensive medical history and physical examination will be performed on all participants during the screening process.

Pregnancy Testing: Serum pregnancy testing will be performed during screening and a urine pregnancy test will be performed at study weeks 4 and 8.

Serum laboratory examination: Complete blood count, electrolytes, and liver function tests will be

performed during the screening process.

Urinalysis: Laboratory urinalysis (glucose, protein, ketones, pH, specific gravity, microscopic analysis) will be performed during the screening process.

Urine Toxicology: Urine samples for toxicology will be collected under directly observed conditions during screening and study weeks 4, 8, and 12 to detect any non-alcohol substance use.

Vital Signs: Temperature, pulse, and blood pressure will be measured at every study visit for data collection and safety monitoring purposes.

Interviews:
Alcohol Timeline Follow-Back (TLFB-A): The alcohol timeline Followback method (Litten and Allen 1992) will gather self-reported alcohol use data.

Clinical Global Impression Scale-Observer (CGI): The CGI–Severity and –Improvement scales (Guy 1976) will be used to measure the overall clinical status of the subject and change from baseline.

Clinical Institute Withdrawal Assessment-Alcohol (CIWA-Ar): The CIWA-Ar (Sullivan et al. 1989), a 10-item scale, is the most widely-used measure of alcohol withdrawal symptoms.
Hamilton Anxiety Scale (HAMA): The HAM-A (Hamilton 1959) is a 14-item instrument widely used to measure current anxiety symptoms.

SAFTEE: The Systematic Assessment for Treatment and Emergent Events (SAFTEE) modified for the COMBINE study (Johnson et al. 2005) will be performed at each study visit.

Psychiatric Evaluation and Diagnosis: The MINI International Neuropsychiatric Interview will be performed during screening as part of a complete psychiatric diagnostic assessment.

Structured Pill Count Interview: The Structured Pill Count Interview is a Timeline Follow-Back assessment of study medication compliance accounting for each dose of prescribed study medication.

Self-Report:
The Quality of Life, Enjoyment and Satisfaction Questionnaire-Short Form (QLES-Q-SF): The QLES-Q-SF is a well validated and widely used 16-item self-report questionnaire that measures the quality of social and occupational functioning (Endicott et al., 1993), satisfaction with physical functioning, household duties, work, leisure, social support and relationships, subjective feelings, study medication.

Clinical Global Impression-Self (CGI-S): The CGI-Self is a 2-item scale that asks the subject to rate their current level of symptoms and change from baseline (Ecdeu 1976).

Medical Outcomes Study Sleep Measure (MOS): A 12-item measure for characterizing the quality of sleep (Hays et al. 2005).

Obsessive Compulsive Drinking Scale (OCDS): A 14-item questionnaire that assesses aspects of alcohol

craving (Anton et al. 1995).

Please see table of study assessments for complete detail of assessments.
Please attach copies, unless standard instruments are used
study assessments.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
Pregabalin
Manufacturer and other information

Manufacturer: Pfizer
Other information: Lyrica

The generic Pregabalin is manufactured by 20 companies.

Please note there are currently 66 brands of generics of Pregabalin.

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

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 during week 1. 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 week 1 of the outpatient phase.
Treatment to be provided at the end of the study
At the conclusion of the study, 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
The primary effective treatments for alcohol use disorder are behavioral treatments and FDA approved medications. The efficacy of pregabalin pharmacotherapy for individuals with alcohol use disorder is unknown. Participants in both arms of the proposed study will receive a supportive behavioral treatment with known benefit, although clinical trial participation is a more restricted treatment environment than community-based clinical treatment. Several psychotherapy methods have been shown to be effective in treating alcohol use disorder including CBT, 12-step facilitation, and Motivational Enhancement Therapy (MET). During the study, participants are permitted to seek additional help from other providers (therapists and physicians outside of the study) which will be tracked using the modified treatment services review. Patients are informed that they may request referral for other treatment options and if participants condition worsen (see trial exit criteria), participants will be referred for clinical treatment.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Participants may or may not benefit from this study. A major risk of research participation is related to drug administration. The maximal recommended dose of pregabalin is 600 mg/day and in the proposed study pregabalin will be administered in doses of up to 600 mg/day with a maximum of a one-week supply of medication supplied to a patient at a time Most common adverse reactions (greater than or equal to 5% and twice placebo) in adults are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and thinking abnormal (primarily difficulty with concentration/attention). Pregabalin is eliminated from the systemic circulation by renal excretion as unchanged drug. Pregabalin is not appreciably metabolized in humans. There are no known significant hepatic drug-drug interactions with pregabalin. Coadministration of pregabalin and opioids, such as morphine or hydrocodone, may lead to increased serum pregabalin levels which in turn may result in CNS depression (e.g., increased somnolence). There are no known long-term

risks of pregabalin. Antiepileptic drugs, such as pregabalin, should not be discontinued abruptly because of the risk of seizures or other adverse effects such as anxiety, insomnia, pain and sweating. Another important risk is the potential for increased intoxication or sedation when alcohol or other substances are combined with pregabalin. Alcohol and pregabalin both cause sedation and ataxia, and the combination of both agents may lead to additive and unpredictable effects. The combination of pregabalin and alcohol might impair a patient's ability to drive or operate heavy machinery.

Pregabalin is of unknown risk to a fetus. There are no adequate and well-controlled studies of pregabalin in pregnant women. Female participants who are currently engaging in sexual activity with males will be required to use adequate methods of birth control (condom with spermicide, diaphragm with spermicide, oral contraceptive pills). Serum pregnancy tests will be evaluated at baseline and monthly throughout the trial. If a patient does become pregnant, she will be withdrawn from study medication and will be offered continued non-pharmacological treatment (i.e., psychotherapy.)

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. The primary source of study related risks in clinical trials of medications stem from the medication itself.

Another important risk is that related to alcohol withdrawal. Participants in this study will have a diagnosis of alcohol use disorder and will be drinking substantial amounts of alcohol per week at entry into the study (see entry criteria described in the research plan). While the exclusion criteria and ongoing assessments are designed to identify those subjects at risk for developing moderate-to-severe physiological alcohol withdrawal, participants nonetheless are at risk for developing moderate-to-severe alcohol withdrawal. Alcohol withdrawal, particularly if untreated, can be a serious medical illness requiring hospitalization, and rarely can result in seizures and/or delirium. The efficacy of pregabalin for the treatment of alcohol withdrawal is not yet definitively known.

The use of riboflavin in all study medication (i.e., both active medication and placebo) is unlikely to pose any risk. The limited capacity to absorb orally administered riboflavin precludes its potential for harm. Riboflavin intake of many times the FDA recommended daily allowance is without demonstrable toxicity. There are no known cases of riboflavin toxicity.

Participants will receive cash compensation and incentives during the study that could pose a risk of using the cash to buy alcohol.

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 participants. 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.

Describe procedures for minimizing risks

1) Screening Procedures

In order to minimize the risk associated with the study, subjects undergo a comprehensive medical and psychiatric evaluation during the screening procedure. The baseline medical evaluation consists of a physical examination, blood chemistry profile (including liver function tests), complete blood count, urinalysis, serum pregnancy test, urine toxicology and is designed, along with the clinical history, to detect chronic and/or unstable medical illnesses. A comprehensive psychiatric assessment is performed during the

screening process, and is intended to detect and assess all past and current psychiatric disorders. The eligibility criteria (see above) are designed to minimize the medical and psychiatric risks to participants by excluding those for whom participation would place them at an increased risk. Special attention will be given to patient's concurrent use of medications. Participants on medications that meet exclusion criteria will not be included in the study.

2) Study Procedures
Participants will be informed about the possible side effects and risks (listed above) of taking pregabalin both alone and in combination with other medications, alcohol, or illicit drugs through extensive discussions with staff psychiatrist(s) during the consent process. Participants will be told to contact the clinic if they experience any adverse effects and given the number for the 24-hr physician on-call. All participants, both those not taking and taking concurrent medications, will be monitored closely throughout the study for possible signs and symptoms of intoxication and potential for medication misuse. Participants' mental status and physical health are monitored weekly during the study period by a psychiatrist. Vital signs will be obtained at each study visit. At clinic visits, a physician will assess participants for signs and symptoms of adverse effects of pregabalin, noting which if any symptoms are present, the severity of the symptoms, make adjustments to study medication dose, discontinue study medication, or withdraw participant(s) from the study if needed.

Female participants who are engaging in sexual activity with men must use adequate methods of contraception which will be discussed repeatedly during the screening process. Serum pregnancy tests will be conducted during screening and urine pregnancy tests will be performed monthly during the study. If a female participant does become pregnant or wishes to become pregnant, study medication will be immediately discontinued, she will be withdrawn from the study, and offered continuing nonpharmacological treatment (psychotherapy).

Alcohol withdrawal will be assessed at each study visit using the Clinical Institute Withdrawal Alcohol (CIWA-AR). Anxiety and drinking will be assessed weekly.

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.

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.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
A certificate of confidentiality will be in place for this study.

To avoid breach of confidentiality, participants' names will appear only on a consent form, a telephone screening form and a "key" form kept by the PI in a locked cabinet. All forms that contain identifying information will be kept double locked (i.e., in a locked cabinet, in a locked room) to maintain their security. All study data forms will contain only the participant's unique study identification number, using a reference system maintained by the PI. Completed study forms will be kept in a locked cabinet, the key to which will be available only to the PI and study research staff. Participant visits will be scheduled, and no information about the participant will be provided to anyone (except in emergencies as defined above) in

person or by telephone. Confidentiality will also be maintained for electronic data sources.

Participants will be informed of alternatives to participation in the proposed trial, including referrals in the community for psychotherapy, group treatment, residential or inpatient, or medical treatment.

At STARS we use coded records (i.e., initials and numbers), store signed consent forms in a locked file cabinet, and try to maintain confidentiality to the best of our abilities. Only coded records are 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, acknowledge to potential participants that we cannot assure that their alcohol and substance use histories and other personal records might not become known.

Upon entry to the study, the participant is asked to provide the contact information of a family member or friend who would be able to locate the individual in case of emergency. The participant is informed that providing this information is entirely voluntary and that study participation is not contingent on permitting research study staff to contact a family member or friend if necessary. The subject, if he or she agrees, will then inform the individual that they may be contacted by the study staff. Only after the subject has informed the individual about the possible contact by the staff will the contact information be provided and the consent form addendum be signed.

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' alcohol use and associated symptoms may improve with study participation. A complete physical and psychiatric evaluation will be performed. Other patients with alcohol dependence may gain from the knowledge obtained from conducting this study. Given the limited medication treatment options available for patients with alcohol dependence, the development of additional pharmacotherapy options would be of great public health benefit. We believe that measures described above to minimize risks for participants make the balance between risk to participants and the potential benefit to participants and others reasonable.

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: Participants will receive $6 per visit for transportation expenses and $10 each week for returning there medication bottle. Participants who attend all study visits and return all study medication bottle could earn a maximum of $228 ($138 in cash for transportation costs and $90 in cash for pill bottle returns).

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