Study: AN OPEN-LABEL PILOT STUDY OF PREGABALIN AS TREATMENT FOR ALCOHOL USE DISORDE

PI: Dr. John Mariani

IRB: 7491

NCT#: NCT03256253

Protocol Date: June 28, 2017

NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

June 28, 2017

TO: Dr. John Mariani

FROM: Dr. Edward Nunes, Co-Chair, IRB
Dr. Laurence Greenhill, Co-Chair, IRB

SUBJECT: **APPROVAL NOTICE**

Your protocol # **7491** entitled **AN OPEN-LABEL PILOT STUDY OF PREGABALIN AS TREATMENT FOR ALCOHOL USE DISORDER** (version date 06-28-17) and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **June 28, 2017 to April 30, 2018.** (Reviewed by the Full Board on 05-01-17.)

Consent requirements:

☐ Not applicable:

☐ 45CFR46.116(d) waiver or alteration of consent

√ 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.**

CC: RFMH Business Office (Smithers Foundation)

ENC: CF, HIPAA form

EN/LG/Scr

Protocol Title:
An Open-Label Pilot Study of Pregabalin as Treatment for Alcohol Use Disorder

Version Date:
06/28/2017

Protocol Number:
7491

First Approval:
06/28/2017

Clinic:
Substance Treatment And Research Services (STARS)

Expiration Date:
04/30/2018

Contact Principal Investigator:
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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?
Division on 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 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
✓ Substance Users

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 is currently funded
Source of Funding
Foundation
Sponsor
Smithers Foundation
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
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research
The proposed protocol is an open label outpatient pilot trial of the feasibility and tolerability of pregabalin (Lyrica) in the treatment of alcohol use disorder. Pregabalin is commonly used for the treatment of pain issues such as fibromyalgia (chronic pain in your body), diabetic nerve pain, spinal cord injury nerve, and pain after shingles. We plan to enroll 20 participants in a 9-week trial.The ideal dosing, tolerability, and safety of pregabalin will be tested in outpatients with Alcohol Use Disorder (AUD). The primary objective of the study is to determine the feasibility and tolerability of pregabalin in promoting alcohol abstinence among individuals with an alcohol use disorder.

Background, Significance and Rationale

Background, Significance and Rationale

Alcohol Use Disorder (AUD) is a common substance use disorder (Regier et al. 1990, Kessler et al. 1994, Grant and Harford 1995, Grant et al. 2004, Kessler et al. 2005, Kessler et al. 2005) responsible for substantial morbidity, mortality (McGinnis and Foege 1999, Mokdad et al. 2004), and economic costs in the U.S. (Harwood 2000). A notably absent option among the available pharmacotherapies for alcohol dependence is a medication that can be administered to actively drinking outpatients that protects against withdrawal and promotes abstinence.

The neuroexcitatory state associated with alcohol withdrawal and the post-acute withdrawal period of neuroadaptation (also known as “protracted withdrawal”) is characterized by insomnia, anxiety, and alcohol craving (Myrick et al. 2001). Emergence of these symptoms, which can be relieved by alcohol consumption, may be associated with relapse drinking in newly abstinent individuals. Because a reduction or cessation of alcohol consumption by an alcohol-dependent individual results in neuroexcitation, neuroinhibitory agents, such as pregabalin, are logical potential therapeutic strategies.

Most pharmacotherapy clinical trials for alcohol use disorders can be considered relapse prevention trials, as they have been conducted in abstinent, recently detoxified patients, and the evidence suggests that the efficacy of two of the FDA-approved medications for AUD (naltrexone and acamprosate) may depend on baseline abstinence (Garbutt et al. 2005, Anton et al. 2006). Other studies (Johnson et al. 2000, Johnson et al. 2003, Johnson et al. 2007) that have been conducted in individuals actively drinking can be considered

abstinence initiation trials (Swift 2003), where the primary measure of efficacy was a reduction in alcohol consumption from baseline. A medication with demonstrated efficacy in actively drinking alcohol-dependent outpatients would have greater clinical applicability than a medication that is only efficacious in individuals who have already achieved abstinence. Since pregabalin can be titrated quickly to clinically relevant doses (300 mg/day in one week), an immediate or early effect of pharmacotherapy should be neuroinhibition.

The development of safe and effective pharmacotherapies for alcohol dependence remains an important public health need. A significant gap in the AUD pharmacotherapy armamentarium exists; no agent has been identified that can be safely administered to actively drinking outpatients to treat withdrawal, promote abstinence, and reduce the risk of relapse. No current pharmacotherapy for alcohol dependence meets these criteria. The proposed project builds on our promising pilot data (see preliminary studies) testing gabapentin as an abstinence initiation strategy for alcohol dependence. The proposed trial aims to study the ideal dosing, tolerability, and safety of pregabalin when administered to actively drinking patients with AUD. This would be the first abstinence initiation trial using pregabalin.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Primary Outcome Measures

1) **Maximum dose pregabalin**: Defined as the highest amount of medication per day maintained for a 7 day period.

2) **Pregabalin Tolerability**: Adverse effects, as measured by the Systematic Assessment for Treatment and Emergent Events (SAFTEE), will calculated by both a symptom count per week and over the course of the study period. The relationship of adverse effects on compliance and outcome will be assessed.

Secondary Outcome Measures

1) **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

2) **The percent days abstinent** will be lower at the end of the trial as compared to baseline.

3) **Symptoms of alcohol withdrawal** will be reduced as compared to baseline.

Exploratory outcome measures

1) Other Alcohol use measures, as measured by the TLFB, including Heavy Drinking Days, Drinks/ Day, and percent days abstinent.

2) Alcohol craving—as measured by the OCDS.

3) Sleep disturbance—as measured by the MOS-Sleep

4) Anxiety symptoms—as measured by the HAM-A

Hypotheses testing:

1) ***Primary Hypothesis***: The mean maximum tolerated dose and mean adverse symptoms count will be calculated.

2) ***Secondary Hypotheses***: Paired-samples T tests will be used to compare baseline assessments to end-of-study assessments for continuous variables (e.g., craving or withdrawal scores) and the chi-square test will

be used for variables reported as proportions (e.g., percent days abstinent, proportion heavy drinking days).

Description of Subject Population

Sample #1

Specify subject population
Adults with AUD
Number of completers required to accomplish study aims
10
Projected number of subjects who will be enrolled to obtain required number of completers
20
Age range of subject population
18-65

Gender, Racial and Ethnic Breakdown
We plan to enroll 20 participants into the study. Both males and females will be recruited. All eligible participants are accepted; however, past experience with recruitment at STARS suggests that the approximate gender distribution for this study will likely be 20% female and 80% male. Previous and ongoing studies at STARS have had samples comprised of approximately 50% Caucasians, and 50% ethnic minorities distributed as 24% African-American and 22% Hispanic-American, and 4% other. We anticipate a similar representation in this project. We will make every effort to recruit minority patients in order to ensure the generalizability of our findings to the overall treatment population.
Description of subject population
We plan to enroll 20 participants into the study who meet criteria for current AUD.

Recruitment Procedures

Describe settings where recruitment will occur
All screening and study procedures will occur at the Substance Treatment and Research Services (STARS) of the Division on Substance Abuse (STARS Downtown) situated on 3 Columbus Circle, 14th Floor, Suite 1408, NY, NY 10019
How and by whom will subjects be approached and/or recruited?
Screening for this study will be covered by the Substance Treatment and Research Service (STARS) umbrella screening protocol #6582R (PI: John Mariani, MD). Trained research assistants and administrative assistants under the supervision of the principal investigator conduct the initial phone screening. Under protocol #6582R, patients who contact STARS interested in research trial participation are informed that they will be asked questions of a personal nature and asked to provide verbal consent for such questions. A "phone screen" form is completed by the phone screener, which asks basic demographic

information, contact information (for scheduling purposes) and description of substance use to determine whether an in-person evaluation appointment is appropriate. Individuals are also informed that if they make an initial screening appointment this “phone screen” information will be forwarded to the clinician to facilitate the first meeting.

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

How will the study be advertised/publicized?

We will recruit individuals with AUD 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 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 in-person evaluation appointment is appropriate. Individuals are also informed that if they make an initial screening appointment this “phone screen” information will be forwarded to the clinician to facilitate the first meeting.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Adults with AUD
Create or insert table to describe the inclusion criteria and methods to ascertain them

1.Meets DSM-5 criteria for current alcohol use disorder	MINI International Neuropsychiatric Interview for DSM-5; psychiatric evaluation
2. 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
3. Between the ages of 18 and 65	Demographics
4. Able to provide informed consent and comply with study procedures	MD assessment

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

1. 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.	MINI International Neuropsychiatric Interview for DSM-5; psychiatric evaluation
2. Subjects receiving psychotropic medication treatment	Medical history; psychiatric evaluation
3. Evidence of moderate-to-severe alcohol withdrawal (CIWA-Ar $\geq$ 13)	Medical evaluation
4. History of alcohol withdrawal seizures or alcohol withdrawal delirium	Medical history
5. History of allergic reaction to candidate medication (pregabalin)	Medical history
6. Pregnancy, lactation, or failure in females patients to use adequate contraceptive methods	Medical history; serum HCG
7. Unstable physical disorders which might make participation hazardous	Medical history; physical examination; ECG; laboratory testing
8. Subjects who have a current DSM-5 diagnosis of moderate or severe substance use disorder, with the exception of alcohol, nicotine and caffeine use disorders. A diagnosis of a mild substance use disorder will not be exclusionary, as long as the current primary substance use disorder is alcohol.	MINI International Neuropsychiatric Interview for DSM-5; psychiatric evaluation; urine toxicology
9. Are legally mandated to participate in alcohol use disorder treatment program	Self-report
10. Cognitively impaired	psychiatric interview; MMSE will be completed on all

individuals over 60 years old

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6582R
Describe Study Consent Procedures
Screening for this study will be covered by the Substance Treatment and Research Service (STARS) umbrella screening protocol #6582R (PI: John Mariani, MD). Trained research assistants and administrative assistants under the supervision of the principal investigator conduct the initial phone screening. Under protocol #6582R, patients who contact STARS interested in research trial participation are informed that they will be asked questions of a personal nature and asked to provide verbal consent for such questions. A "phone screen" form is completed by the phone screener, which asks basic demographic information, contact information (for scheduling purposes) and description of substance use to determine whether an in-person evaluation appointment is appropriate. Individuals are also informed that if they make an initial screening appointment this “phone screen” information will be forwarded to the clinician to facilitate the first meeting.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Bisaga, Adam, MD
Brezing, Christina, MD
Dakwar, Elias, MD
Evans, Elizabeth, MD
Kidd, Jeremy
Levin, Frances, MD
Luo, Sean, MD
Mariani, John, 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 20 men and nonpregnant women with AUD who report 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. The daily minimum drinking requirements are consistent with the commonly accepted definition of "binge drinking." A minimum requirement of having a heavy drinking episode 4 days a week would select for a population of individuals who are drinking excessively more days than not. An exclusion threshold CIWA-Ar score of $\geq$ 13 is set to balance the need to protect participants from the consequences of untreated severe alcohol withdrawal symptoms and the need for the enrolled patients to have alcohol withdrawal symptoms of sufficient severity to detect between group differences. During the first two weeks of the study participants will be monitored frequently for the development of severe alcohol withdrawal symptoms. The gabapentin pilot study used an exclusion cut-off of CIWA-Ar score of $\geq$ 13 and there were no serious adverse events and no participants were removed from the trial due to the development of alcohol withdrawal, suggesting that a CIWA-Ar eligibility and drop-out threshold $\geq$ 13 combined with careful monitoring will appropriately protect participants from the risk of untreated alcohol withdrawal symptoms.

Design Overview: In a 9-week open label outpatient pilot trial, the ideal dosing, tolerability, and safety of pregabalin will be tested in 20 outpatients with AUD. The specific aims of the project are to determine in AUD outpatients 1) Pregabalin will be well tolerated and safe when used as an abstinence-initiation agent in AUD outpatients in doses ranging up to 600 mg per day. 2) the ideal target dose range and tolerability of pregabalin pharmacotherapy. Secondary outcome measures will be the end-of-study proportion of heavy drinking days and percent days abstinent compared to baseline. Exploratory measures include: 1) alcohol use as measured by secondary outcomes such as amount of drinks per day; and 2) the symptoms of alcohol withdrawal.

Medication: Pregabalin will be prepared by our pharmacy at the NYSPI. Pregabalin will be administered in 75 mg and 100 capsules. Pregabalin will be titrated over a 3-week period to the FDA maximum (600 mg per

day) or the maximum tolerated dose (see table 1). 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. At each weekly visit the psychiatrist orders the dose of medication for the coming week according to the schedule. Dose reductions for tolerability will be made by the research psychiatrist in coordination with the research pharmacy. If a patient does experience any uncomfortable side effects, the dose will not be raised, and if necessary, the dose will be lowered. During week 9 patients will be tapered off pregabalin. Medication will be dispensed in child-resistant bottles containing a one-week supply of medication.

Currently the study is run under the NYS Controlled Substance license # 0400081 held by the NYS OMH and the DEA Researcher Registration # PN0093461 held by the NYSPI Pharmacy Department. As soon as 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.

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.

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 open-label investigation.

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). This psychosocial intervention facilitates compliance with study medication and other study procedures, promotes abstinence from marijuana and other substances,

and encourages mutual-support group attendance. Dr. Mariani will provide ongoing supervision to other study physicians to prevent therapeutic drift. All study psychiatrists will be trained in providing Medical Management and refresher training sessions will be provided every 6 months. As director of Columbia's Substance Treatment and Research Service, Dr. Mariani has extensive experience conducting and supervising Medical Management and other similar medication adherence focused psychosocial intervention models.

Study Visits: Study visits will occur daily for the first 4 days of the study period. During the second week, patients will be asked to attend 3 study visits. During the remainder of the 8-week study period, study visits will occur twice weekly. There will be one visit during the taper week (week 9). There will be final post-taper visit after study medication is discontinued (week 10). One visit per week will be with the research psychiatrist. Participants will receive $10 per visit for transportation expenses.

You can upload charts or diagrams if any
table 1.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 2 consecutive weeks
2. Development of evidence of moderate-to-severe alcohol withdrawal (CIWA-Ar > 13) 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 the participant becomes pregnant

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 (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 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

Physiological Measures

1. **Alcohol Breath Testing**: Alcohol breath testing will be performed at every study visit.
2. **Medical History and Physical Exam**: A comprehensive medical history and physical examination will be performed on all participants during the screening process.
3. **Pregnancy Testing:** Serum pregnancy testing will be performed during screening and a urine pregnancy test will be performed at study weeks 4 and 8.
4. **Serum laboratory examination**: Complete blood count, electrolytes, and liver function tests will be performed during the screening process.
5. **Urinalysis**: Laboratory urinalysis (glucose, protein, ketones, pH, specific gravity, microscopic analysis) will be performed during the screening process.
6. **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.
7. **Vital Signs**: Temperature, pulse, and blood pressure will be measured at every study visit for data collection and safety monitoring purposes.

Interviews

1. **Alcohol Timeline Follow-Back (TLFB-A)**: The alcohol timeline Followback method (Litten and Allen 1992) will gather self-reported alcohol use data.
2. **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.
3. **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.
4. **Hamilton Anxiety Scale (HAMA)**: The HAM-A (Hamilton 1959) is a 14-item instrument widely used to measure current anxiety symptoms.
5. **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.
6. **Psychiatric Evaluation and Diagnosis**: The MINI International Neuropsychiatric Interview will be performed during screening as part of a complete psychiatric diagnostic assessment.
7. **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.
8. **Modified Treatment Services Review (TSR)**: The Modified Treatment Services Review is an 18-item questionnaire modified from the Treatment Services Review (McLellan et al. 1992) that assesses the past week exposure of the subject to health care and substance use disorder treatment.

Self-Report

1. **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).
2. **Medical Outcomes Study Sleep Measure (MOS)**: A 12-item measure for characterizing the quality of sleep (Hays et al. 2005).
3. **Obsessive Compulsive Drinking Scale (OCDS)**: A 14-item questionnaire that assesses aspects of alcohol craving (Anton et al. 1995).

Please attach copies, unless standard instruments are used
schedule of study assessments 4-18-17.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

Other name: Lyrica
Manufacturer: Pfizer

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. Medical management therapy is an abstinence-focused supportive psychotherapy condition developed for substance use disorder pharmacotherapy clinical trials and will begin in week 1 of the treatment study. 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 treatment study.
Treatment to be provided at the end of the study

At the conclusion of the 9-week protocol, the participants will be offered supportive therapy for at least one additional month or until an appropriate referral for on-going treatment is made.

If a patient found the medication to be beneficial, they will be given an appropriate referral for ongoing treatment.

Clinical Treatment Alternatives

Clinical treatment alternatives
Participants will be informed of alternatives to participation in the proposed trial. The alternative procedures available are individual counseling by other clinicians, 12-step facilitation, or more intensive treatment for heavy drinking such as inpatient or outpatient detoxification, inpatient rehabilitation, or intensive outpatient programs. Additionally there are a number of medication that may aid in relapse prevention, including naltrexone (Revia) and disulfiram (Antabuse). 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

The major risk of research participation is related to drug administration. Pregabalin will be administered up to a maximum of 600mg per day. Side effects most commonly associated with pregabalin include: drowsiness, dizziness, dry mouth, constipation, difficulty concentrating, swollen arms/legs, and weight gain. Some serious side effects, which are unlikely, include: blurred vision, unusual bleeding/bruising, unsteadiness, confusion, muscle pain/tenderness/weakness, swelling of hands/legs/feet, signs of kidney problems (such as change in the amount of urine). Rare side effects include: rash, itchiness, trouble breathing, and changes in a participants mood, thoughts, or behavior such as depression or suicidal ideation. All participants are fully informed of the side effect that they might experience.
Participants may be at greater risk if they self-administer other drugs that interact with the study medications. To the extent that they do not reduce or eliminate alcohol use, risk may increase. It is not considered safe during pregnancy or breast-feeding. Therefore, female participants will be required to use adequate methods of birth control. Serum pregnancy will be completed at baseline and urine pregnancy tests will be evaluated at week 4 and 8. If a female patient becomes pregnant, she will be withdrawn from study

medication and offered continuing non-pharmacological treatment (i.e., psychotherapy) with STARS until the conclusion of treatment or given referrals to other treatment centers.

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. All participants will be informed that they can refuse to complete anything they are uncomfortable completing.

Participants will complete a blood draw at screening which can cause slight discomfort and bruising. They will be warned prior to completion of these facts.

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. The exclusion criteria are designed to minimize the medical and psychiatric risks to participants as discussed above, including risks of adverse events and side effects. All patients will be informed of the possible side effects and risks through extensive discussions with the research psychiatrist during the consent process.

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

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.
Subjects will 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. The maximum amount over the 9 weeks a participant may potentially earn for attending all study visits is $300 ($210 (19 study visits during the 8 weeks plus we will ask participants to return for 1 visit in week 9 to gather complete data from week 8 and once in week 10 after titration off of medication is complete) for travel and $90 for bottle return).

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