NCT02884908

Pharmacogenetic Treatment With Anti-Glutaminergic Agents for Comorbid PTSD & AUD

Study Protocol

October 23, 2023

Accessed 10/23/2023

Last approved by IRB: 5/4/2023 – Annual Continuing Review

Introduction Page

1 * Abbreviated Title:
Anti-Glutaminergic Agents for Comorbid PTSD & AUD

2 * Full Title:
Pharmacogenetic Treatment with Anti-Glutaminergic Agents for Comorbid PTSD & AUD

3

* Select Type of Submission:

- (●) **IRB Application**
- ( ) Humanitarian Use Device (for FDA approved Indication & non-research purposes ONLY)
- ( ) Single Patient Expanded Access (pre-use)
- ( ) Single Patient Emergency Use (post-use)
- ( ) Unsure if this proposal requires IRB review (Not Human Subject Research)

Note: The Type of Submission cannot be changed after this application has been submitted for review.

4 Original Version #:

Research Team Information

1 * Principal Investigator - Who is the PI for this study (person must have faculty status)? ***Faculty status is defined as being a full-time (>51% effort) faculty member holding one of the following titles at UM: Professor; Associate Professor; Assistant Professor.***
Melanie Bennett

CITI Training: ID00006944

1.1 * Does the Principal Investigator have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

2 Point of Contact - Who is the alternative point of contact for the PI? This person can be a study coordinator or any other study team member. In case the IRB cannot contact the PI, this person is a secondary person to contact:
Brian Brandler

CITI Training: ID00010434

2.1 Does the Point of Contact have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

3 Other Team Members - list all additional members of the research team for this study. DO NOT include the PI or POC in this list:

	Name	Edit Submission	cc on Email	Research Role	Has SFI?	CITI Training
View	Daniel Roche	yes	no	Sub-Investigator	no	ID00009320
View	Wendy Potts	yes	no	Research Team Member	no	ID00008918
View	Belinda Kauffman	no	no	Research Team Member	no	ID00009489
View	Clayton Brown	no	no	Sub-Investigator	no	ID00000679
View	David Gorelick	yes	yes	Sub-Investigator	no	ID00007376
View	Aaron Greenblatt	no	no	Research Team Member	no	ID00008817
View	Florencia Schillaci	no	no	Other	no	ID00011561
View	Eric Weintraub	no	no	Research Team Member	no	ID00003461
View	Chamindi Seneviratne	no	no	Sub-Investigator	no	ID00005865
View	Bankole Johnson	no	no	Other	no	ID00005763
View	LAN LI	no	no	Research Team Member	no	
View	Anne Naclerio	no	no	Research Team Member	no	ID00012810
View	Tshaka Cunningham	no	no	Research Team Member	no	
View	Daniel Brady	no	no	Research Team Member	no	

IMPORTANT NOTE: All research team members (including PI) must have current CITI and HIPAA training completed.

Resources

If this study is a collaborative UM/VA study, please clarify which resources are being used at each institution.

1 * Describe the time that the Principal Investigator will devote to conducting and completing the research:
Dr. Bennett will devote 20% effort.

2 * Describe the facilities where research procedures are conducted:
UM Participants: Participant screening and testing will occur at either the Maryland Psychiatric Research Center Center (MPRC) at 55 Wade Ave., Catonsville, MD, 21225 or the University of Maryland Medication Center General Clinical Research Center (UMMC GCRC). The UMMC GCRC is a resource for all UMB research. This protocol is approved to conduct research activities there.

3 * Describe the availability of medical and/or psychological resources that subjects might need as a result of anticipated consequences of the human research:
Study staff with clinical expertise and study clinicians are always present during clinic hours and will respond promptly to any participant needs.

For appointments at the MPRC: If additional evaluation or treatment are needed, on-site clinicians will be called to meet with the participant. In a severe acute emergency, 911 will be called. The closest hospital is 3 miles away (St. Agnes Hospital).

For appointments at UMMC GCRC: If additional evaluation or treatment are needed, participants can be referred to the Emergency Department at UMMC. The GCRC is located on the 10th floor of the hospital building, the same building as the Emergency Department.

4 * Describe the process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions:
Study staff working on this protocol will be specially trained in working with participants with serious mental illness. Their assigned duties on this project will be described to them in detail. They will become very familiar with the protocol through ongoing study team meetings and trainings. All of our staff are extensively trained on obtaining informed consent and the study assessments. Study staff practice study procedures beforehand and are observed a number of times prior to meeting with a research participant alone. Furthermore, they are observed on a quarterly basis obtaining informed consent and conducting the study assessment.

Sites Where Research Activities Will Be Conducted

1 * Is this study a:

- ○ Multi-Site
- ● **Single Site**

2 * Are you relying on an external IRB (not UM) to be the IRB of Record for this study?

- ○ Yes ● **No**

3 * Are any other institutions/organizations relying on UM to be the IRB of Record for this study?

- ○ Yes ● **No**

3.1 Attach the applicable regulatory documents here (i.e., IRB Authorization Agreement (IAA), FWA, local ethics approval, other IRB approvals, etc.). Final UM approval will be contingent upon final execution of all required regulatory approvals:

Name	Created	Modified Date

There are no items to display

4 * Is UM the Coordinating Center for this study? (Applicable for multi-site studies. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project.)

- ● **Yes** ○ No

5 Is VA the Coordinating Center for this study? (Applicable for Collaborative studies between the VA, UM and other sites. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project)

- ○ Yes ● **No**

6 * Institution(s) where the research activities will be performed:

- ☐ University of Maryland, Baltimore
- ☐ University of Maryland, Upper Chesapeake Kaufman Cancer Center
- ☐ VAMHCS
- ☑ **UMB School of Medicine**
- ☐ Marlene and Stewart Greenebaum Cancer Center
- ☐ University Physicians Inc.
- ☐ Shock Trauma Center
- ☑ **General Clinical Research Center (GCRC)**
- ☑ **Maryland Psychiatric Research Center (MPRC)**
- ☐ Johns Hopkins
- ☐ International Sites
- ☐ UMB Dental Clinics
- ☐ Center for Vaccine Development
- ☐ Community Mental Health Centers
- ☐ Private Practice in the State of Maryland

- [ ] Institute of Human Virology (IHV) Clinical Research Unit
- [ ] Joslin Center
- [ ] UMB Student Classrooms
- [ ] National Institute of Drug Abuse (NIDA)
- [ ] National Study Center for Trauma and EMS
- [ ] Univ of MD Cardiology Physicians at Westminster
- [ ] Nursing Homes in Maryland
- [ ] University of Maryland Biotechnology Institute
- [ ] Maryland Department of Health
- [ ] Maryland Proton Treatment Center
- [ ] Mount Washington Pediatric Hospital
- [ ] Institute of Marine and Environmental Technology (IMET)
- [ ] Other Sites
- [x] **University of Maryland Medical System (Select below)**

* UMMS Sites:

- [x] **University of Maryland Medical Center**
- [x] **UMMC Midtown Campus (formerly Maryland General Hospital)**
- [ ] UM St. Joseph Medical Center
- [ ] UM Baltimore Washington Medical Center
- [ ] UM Capitol Region Health
- [ ] UM Charles Regional Medical Center
- [ ] UM Shore Medical Center at Easton
- [ ] UM Shore Medical Center at Chestertown
- [ ] UM Shore Medical Center at Dorchester
- [ ] UM Shore Emergency Center at Queenstown
- [ ] UM Shore Regional Health
- [ ] University of Maryland Rehabilitation & Orthopaedic Institute (formerly Kernan Hospital)
- [ ] UM Upper Chesapeake Health
- [ ] UM Upper Chesapeake Medical Center
- [ ] UM Harford Memorial Hospital
- [ ] University of Maryland Community Medical Group

UM Coordinating Center

You indicated that UM is the Coordinating Center for this multi-site study.

2.1 *Describe the processes to ensure communication among sites.

Things to consider including in the communication plan:

- all sites have the most current version of the protocol, consent document, etc.
- all required approvals have been obtained at each site (including approval by the site's IRB of record).
- all modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
- all engaged participating sites will safeguard data as required by local information security policies.
- all local site investigators conduct the study appropriately.
- all non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

All study staff will be trained, supervised, and monitored by the PIs, physicians, and study coordinator. Trained study staff, based at UM, will see participants at all sites. All sites will have the most current versions of the protocol, consent forms, and SOPs. All required approvals will be obtained at all sites and any IRB-approved changes will be communicated to all staff so that they can be implemented across sites. All data will be managed by UM. All non-compliance with the study protocol and any reporting requirements will be done in accordance with local policies and overseen by the study PIs and study coordinator.

2.2 *Describe the method for communicating to engaged participating sites including:

- reportable new information.
- problems.
- interim results.
- the closure of a study.

Trained study staff will meet with participants across sites. All study SOPs will be used across sites. Any IRB-approved changes will be reviewed and approved by local VA R&D before implementation at the VAMHCS.

Maryland Department of Health

You selected "Maryland Psychiatric Research Center" or “Maryland Department of Health” as a research site. Answer the following questions to determine if Maryland Department of Health review is needed.

3.1 * Does this protocol require Maryland Department of Health IRB review?

◯ Yes ● **No**

3.2 If Yes, will the Maryland Department of Health IRB rely on UM IRB as the IRB of record for review of this protocol?

◯ Yes ◯ No

ID: VIEW4DF86705BB800
Name: v2_Maryland Department of Health

Funding Information

1 * Indicate who is funding the study:

- [x] **Federal**
- [ ] Industry
- [ ] Department / Division / Internal
- [ ] Foundation
- [ ] Private
- [ ] State Agency

2 * What portion of the research is being funded? (Choose all that apply)

- [x] **Drug**
- [ ] Device
- [x] **Staff**
- [x] **Participant Compensation**
- [ ] Procedures
- [ ] Other

3 Please discuss any additional information regarding funding below:

DHHS Funded Study

You indicated that this is a Federally funded study.

1 * Is this study sponsored by a Department of Health and Human Services (DHHS) agency?

● **Yes** ○ No

2 You may upload any grant documents here:

Name	Created	Modified Date
R01 AA024760-01 DSM Plan_Revised 4 7 2016.pdf(0.01)	9/11/2016 6:24 PM	9/11/2016 6:24 PM
Johnson R01 Specific Aims.docx(0.01)	9/11/2016 6:23 PM	9/11/2016 6:23 PM
Johnson Abstract R01 AA024760-01.docx(0.01)	9/11/2016 6:18 PM	9/11/2016 6:18 PM
Notice of Award.pdf(0.01)	9/11/2016 6:18 PM	9/11/2016 6:18 PM

ID: VIEW4DF87B9560800
Name: v2_DHHS Funded Study

Federal Agency Sponsor Contact Information

You indicated that this is a Federally funded study.

1

* Agency Name:
NIAAA

* Address 1:
6000 Executive Blvd

Address 2:
402

* City:
Rockville

* State:
MD

* Zip Code:
20852

* Contact Person:
Judy Fox - Grants Management Officer

* Phone Number:
(301) 443-3860

* Federal Agency Email:
jfox@mail.nih.gov

Grant Number 1 (if applicable):
1R01AA024760-01- OR - Check here if Grant 1 is not assigned a number. ☐

If Grant 1 has no number, please provide the following information:

Title of Grant 1:
Pharmacogenetic Treatment with Anti-Glutaminergic Agents for Comorbid PTSD & AUD
PI of Grant 1:
Bankole Johnson

Grant Number 2 (if applicable):
- OR - Check here if Grant 2 is not assigned a number. ☐

If Grant 2 has no number, please provide the following information:

Title of Grant 2:

PI of Grant 2:

Grant Number 3 (if applicable):
- OR - Check here if Grant 3 is not assigned a number ☐

If Grant 3 has no number, please provide the following information:

Title of Grant 3:

PI of Grant 3:

Grant Number 4 (if applicable):
- OR - Check here if Grant 4 is not assigned a number. ☐

If Grant 4 has no number, please provide the following information:

Title of Grant 4:

PI of Grant 4:

Research Protocol

1 * Do you have a research protocol to upload?

- ○ Yes
- ● **No, I do not have a research protocol and will use the CICERO application to enter my study information**

2 If Yes, upload the research protocol:

Name	Created	Modified Date
There are no items to display		

ID: VIEW4E00563F8D000
Name: v2_Research Protocol

Risk Level

What is the risk level of your study? (Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.)

* Choose One:

- ○ Minimal - The probability & magnitude of harm/discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations/tests.
- ● **Greater Than Minimal - Does not meet the definition of Minimal Risk.**

ID: VIEW4E02805225800
Name: v2_Risk Level

Type of Research

1 * Indicate **ALL** of the types of research procedures involved in this study (Choose all that apply):

- [x] **Use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol.**
- [ ] Evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.
- [ ] Use of device(s) whose use is specified in the protocol
- [x] **Psychological/Behavioral/Educational Method or Procedure (i.e., survey, questionnaires, interviews, focus groups, educational tests).**
- [x] **Sample (Specimen) Collection and/or Analysis (including genetic analysis).**
- [ ] Data Collection or Record Review (i.e., chart review, datasets, secondary data analysis).
- [ ] None of the above.

2 * Is this study a clinical trial OR will this study be registered at ClinicalTrials.gov?
A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

(●) **Yes** ( ) No

ID: VIEW4E0280569E000
Name: v2_Type of Research

Lay Summary

1 * Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

Nearly 60% of individuals with posttraumatic stress disorder (PTSD) have a comorbid alcohol use disorder (AUD). This comorbidity is associated with more severe PTSD symptoms, higher rates of psychosocial and medical problems, higher relapse rates, and poorer treatment outcome. Pre-clinical studies have indicated that PTSD and AUD share common molecular underpinnings. In particular, the adaptations in brain neurotransmitter systems in response to chronic excessive drinking (which become evident during alcohol withdrawal) share similarities with PTSD symptoms of re-experiencing the traumatic event and hyper-arousal. These initiate a cycle of relapse into excessive drinking and worsening of PTSD symptoms. Excessive glutamate and reduced gamma- amino butyric acid (GABA) neurotransmitter concentrations were found in various brain regions in individuals with co- morbid PTSD/AUD. The anticonvulsant pregabalin, which increases GABA activity in the brain, has shown preliminary efficacy in reducing drinking in AUD with comorbid generalized anxiety disorder, and improves outcomes from PTSD. Large scale studies with ample statistical power in VA settings and community populations, with diverse combat and non-combat related trauma, are now warranted to evaluate the promising preliminary evidence that pregabalin can improve outcomes for those with AUD and PTSD. An important personalized medicine approach to optimize pregabalin efficacy would be to select individuals with AUD and PTSD with genetic variations that might respond more effectively to pregabalin. We will, therefore, group our target sample by genetic variation.

We will test pregabalin efficacy in reducing both AUD and PTSD symptoms in 2 treatment groups of medication (pregabalin, placebo) x 2 genetic variants (expected to be responsive to medication or non-responsive) in a double- blind, placebo-controlled 14-week clinical trial. We will utilize a large and diverse sample of both genders and individuals with different types of trauma. The sample will include people of African American and European ancestry. Pregabalin dose (and placebo) will be titrated to the target dose (450 mg/day) from baseline to week 3. All participants will receive standardized weekly Brief Behavioral Compliance Enhancement Treatment.

Justification, Objective, & Research Design

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

Nearly 60% of individuals with posttraumatic stress disorder (PTSD) have a comorbid alcohol use disorder (AUD). This comorbidity is associated with more severe PTSD symptoms, higher rates of psychosocial and medical problems, higher relapse rates, and poorer treatment outcome. Pre-clinical studies have indicated that PTSD and AUD share common molecular underpinnings. Particularly, the adaptations in the brain neuro- transmitter systems to chronic excessive drinking that are evident during alcohol withdrawal share similarities with PTSD cluster B and E symptoms (characterized by symptoms of re-experiencing and hyper-arousal), which initiate a cycle of relapse into excessive drinking and worsening of PTSD symptoms. Thus all participants, whether they meet criteria for PTSD or for Other Specified Trauma/Stressor-Related Disorder, will have elevations in both Cluster B and Cluster E symptoms such that the study aims will be relevant for all participants. Excessive glutamate and reduced gamma-amino butyric acid (GABA) neurotransmitter concentrations were found in various brain regions in individuals with co-morbid PTSD/AUD. The anticonvulsant pregabalin (with high affinity for the alpha-2-delta auxiliary site of voltage gated calcium channels), which modulates the effects of the GABA transporter (GAT-1) and increases its density of GABA, has shown preliminary efficacy in reducing drinking in AUD with comorbid generalized anxiety disorder, and improves outcomes from PTSD. Large scale studies with ample statistical power in VA settings and community populations, with diverse combat and non-combat related trauma, are now warranted to evaluate the promising preliminary evidence that pregabalin can improve outcomes for those with AUD and PTSD. An important personalized medicine approach to optimize pregabalin efficacy would be to select individuals with AUD and PTSD with genetic variation at the GAT-1 transporter so as to match its potential therapeutic effects with specific types of individual. In people of African American or European ancestry, variants at the SLC6A1 gene promoter region insertion (i.e., non-insertion/insertion or insertion/insertion (NI/I or I/I) compared with those of Non-insertion/Non-insertion (NI/NI) type have significantly higher levels of GAT-1promoter activity. We will, therefore, group our target sample by genetic variation at the GAT-1 transporter. Because of the low allelic frequency of individuals with the double copy insertion, we will combine these into one group with those with the single copy (i.e., NI/I/II). Mixed ancestry individuals will not be included in this study

We will test pregabalin efficacy in reducing both AUD and PTSD Clusters B or E in 2 treatment groups of medication (pregabalin 450 mg/day and placebo) x 2 genetic variants (NI/I/II vs. NI/NI) in a double- blind, placebo-controlled 14-week clinical trial (screening, 12 weeks of study medication, follow-up call). We will utilize a large and diverse sample that includes both genders and individuals with different types of trauma. After a one-week screening period, pregabalin dose (and placebo) will be titrated to the target dose from baseline to week 3 using a double-dummy procedure to ensure equivalence of capsules received. Participants will be tapered off study medication during the 12th week. All participants will receive standardized Brief Behavioral Compliance Enhancement Treatment at each treatment visit and a follow-up telephone call one week after the end of treatment. Our specific aims are as follows:

Specific Aim 1: Independent of race, to test the hypothesis that AUD/PTSD participants treated with pregabalin will demonstrate a greater reduction in heavy drinking than placebo treated participants.
Specific Aim 2: Independent of race, to test the hypothesis that AUD/PTSD participants treated with pregabalin will demonstrate a greater reduction in PTSD cluster B or E symptoms (or both) than placebo-treated participants.
Specific Aim 3: To test the hypothesis that race will moderate the effects of pregabalin examined in Aims 1 and 2.
Specific Aim 4: To test the hypothesis that the treatment responses to pregabalin specified in Aims 1 and 2 are modulated by genetic variations within SLC6A1 gene in AUD/PTSD in both AA and EA populations.

2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:

This is a randomized, double-blind clinical trial. Participants will be randomized to drug or placebo in a 1:1 ratio, with each medication group also stratified by genotype. All participants will receive the psychoeducational intervention Brief Behavioral Compliance Enhancement Treatment (BBCET).

3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:

In two published studies of adult outpatients with AUD, one a controlled clinical trial comparison with naltrexone (27 participants on pregabalin), the other an open-label series of 31 patients taking pregabalin), pregabalin (150-450 mg/day) significantly reduced alcohol intake in the majority of participants. In the one published placebo-controlled clinical trial of which we are aware, pregabalin (300 mg/day for 6 weeks, 18 participants) significantly reduced PTSD symptoms vs. placebo (19 participants), but did not reduce other anxiety symptoms or depression. Three published case reports/series, involving a total of 11 patients with PTSD, also found that pregabalin treatment (150-45 mg/day), as augmentation of existing anti-depressant treatment, substantially reduced PTSD symptoms in the majority of patients. We are not aware of any study evaluating pregabalin for the treatment of comorbid AUD and PTSD.

Therefore, large-scale studies with ample statistical power in VA settings and community populations, with diverse combat and non-combat related trauma, are now warranted to evaluate this promising preliminary evidence that pregabalin can improve outcomes for those with AUD and PTSD. An important personalized medicine approach to optimize pregabalin efficacy would be to select individuals with AUD and PTSD with genetic variation at the GAT-1 transporter so as to match its potential therapeutic effects with specific types of individual. In people of African American or European ancestry, variants at the SLC6A1 gene promoter region insertion (i.e., non-insertion/insertion or insertion/insertion (NI/I or I/I) compared with those of Non-insertion/Non-insertion (NI/NI) type have significantly higher levels of GAT-1promoter activity. We are not aware of any published using such genetic stratification to evaluate pharmacotherapy for AUD and PTSD.

4 * Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

This trial will shift current research and clinical practice related to PTSD and comorbid AUD. PTSD with comorbid AUD represents a highly prevalent condition that confers serious negative health, relationship, and functional consequences on individuals, families, and societies. An effective intervention must be found, and our work directly addresses this need. We are proposing to test a promising medication that may impact both conditions in a large and diverse sample that includes males and females recruited from community and VA settings with a range of traumatic experiences. Including within our sample participants recruited from both community and VA settings who have experienced diverse forms of trauma will broaden the generalizability (external validity) of this work beyond that of previous studies and ensure that it is applicable to the wide range of individuals who experience PTSD. The split design gives us the ability to test the pregabalin effect on symptom reduction for both PTSD and AUD simultaneously in the first 8 weeks vs. in the following 8 weeks if and how the cessation of drinking affects PTSD symptoms. Moreover, within the same study we test not only pregabalin's effects on drinking, but also its effects on relapse prevention post drinking cessation - both critical concepts in a population of individuals with comorbid PTSD. The choice of cluster B PTSD symptoms and the relapse prevention approach specifically targets the heightened glutaminergic components of these comorbid disorders and optimizes the potential for pregabalin to treat these conditions. Furthermore, we are testing a scientifically and clinically robust personalized medicine approach to the treatment of AUD and PTSD by incorporating prospective selection of the treatment groups by genotype, an approach that can be translated directly to the clinic, whereby patients likely to respond specifically to pregabalin can be identified through genetic screening and then be treated with the medication. Identifying medicine(s) that have a robust therapeutic effect in clinical applications, even for a subgroup of those with AUD, would enhance the perception that AUD can be treated effectively using pharmacotherapy and would increase the search for new (and better) drugs and their novel application. Our prospective pharmacogenetic approach not only allows us, for the first time, to test the independent effects of the genotypes on AUD but also permits a balanced examination of whether the same or a different combination(s) of genotypes is more predictive to pregabalin treatment response to both PTSD and AUD.

Supporting Literature

1 * Provide a summary of current literature related to the research: ***If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.***

Pregabalin (Lyrica®) was FDA-approved in 2004 for the treatment of adult partial onset seizures, diabetic neuropathic pain, and postherpetic neuralgia, and subsequently for fibromyalgia and neuropathic pain associated with spinal cord injury. It is also approved in the European Union and Russia for generalized anxiety disorder; and used off-label for other types of pain, e.g., perioperative pain (1).

Pregabalin has high affinity for the alpha-2-delta auxiliary site of voltage gated calcium channels that modulates the effects of the GABA transporter (GAT-1) and increases density of GABA.

Pregabalin has shown preliminary efficacy in reducing drinking in AUD with comorbid generalized anxiety disorder, and improves outcomes from PTSD.

2 If available, upload your applicable literature search:

Name	Created	Modified Date
Pregabalin PTSD AUD Literature.docx(0.01)	10/21/2016 8:21 AM	10/21/2016 8:21 AM

ID: VIEW4E02805A7E400
Name: v2_Supporting Literature

Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

1 * Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:

The study schedule is attached in Additional Documents.

This is a 14-week study:
Week 1 = in-person screening
Weeks 2-13 = baseline assessment, treatment, post-treatment assessment
Week 14 = follow-up phone call

At the start of each in-person study visit, participants will undergo a breathalyzer test to measure breath alcohol concentration (BrAC). For the consent visit, BrAC must be 0.00 before informed consent procedures can be initiated. If the participant has a BrAC greater than 0.00, he/she will either be: (a) sent home and scheduled to return on another day (when BrAC is over 0.03%), or (b) offered something to eat and water to drink, and then re-do the BrAC after sufficient time has passed to determine if it has dropped to 0.00 (when BrAC is in the range of 0.01-0.03%).

For all other study visits, BrAC will be measured at the start of the visit. (1) All participants with BrAC at or below 0.02% will continue with study assessments. If a participant has a BrAC in the range of 0.02% - 0.04%, study staff will determine if the participant can put forth good effort on the study measures. If judged to be so, the participant will continue with study assessments. If judged to not be so, the participant will either be: (a) sent home and scheduled to return on another day (when BrAC is over 0.06%), or (b) offered something to eat and water to drink, and then re-do the BrAC after sufficient time has passed to determine if it has dropped to or below 0.04% (when BrAC = 0.05%). If a participant decides to leave the study site with a BrAC greater than 0.02% rather than wait or complete the study visit, the research team will make a reasonable effort to reach the participant later in the day to ascertain his/her safety and to encourage him/her to attend the next clinic visit.

I. Telephone Screening

Participants will be recruited through local advertisements in print and broadcast media, through flyers distributed throughout the Greater Baltimore regions, by advertising online and through social media, and by networking with treatment programs in counties within 30 miles of the MPRC. Participants who express interest by responding to any of these means of advertising will be contacted to participate in a screening interview. Prior to eliciting any information, we will describe the nature of the study, including the number of visits to the center, participant protections, and confidentiality. If the called is still interested in participating, we will obtain verbal consent for the telephone screening. Screening questions cover general health, psychiatric history, and alcohol consumption. If, in consultation with the Principal Investigators or their designee, we determine that the applicant is eligible based on this screening, s/he will be invited to come to the clinic for an in-person screening visit. During this scheduling call, we will obtain verbal consent for the BrAC test so that it can be administered immediately upon arrival at MPRC prior to informed consent and study procedures.

II. In-person Screening

At the In-Person Screening, potential participants sign informed consent, complete measures to ensure study eligibility, and complete genetic screening to allow stratification on the tested genotypes. Upon arriving to the visit, participants will undergo a breathalyzer test to ensure a breath alcohol concentration (BrAC) no more than 0.02%, which will be used to assess alcohol intoxication at every visit. Then, they will first complete informed consent. The following measures will be collected at the screening visit:

1. Breath Alcohol test (BrAC). The breath alcohol test result must be 0.000 in order to continue with the informed consent process. Before presenting the consent form for the main study, completing this screening BrAC will ensure that the participant is not under the influence of alcohol when the main study consent document is explained. Participants needs to the BrAC screening (the test result must be less than 0.000) in order to proceed to the main consent process. If the BrAC test result is over 0.000, the individual can either stay until the reading goes down or return on a day when he/she has not consumed alcohol.

2. Informed consent form - Participants will be given the informed consent form to read, after which research staff will review it and provide an explanation of the study protocol, its risks, potential benefits, and alternative treatments. Following resolution of any questions, participants s will be asked to sign the consent form. An entire copy of the signed informed consent form will be given to the participant, who will be reminded that the consent addresses his or her willingness to participate but that the subsequent screening process will determine his/her eligibility to do so. Further, the participant will be reminded

3. Subject locator form - asks participants to identify people who will know the whereabouts of the participant to assist in locating the participant during treatment if needed.

4. Demographic form - includes assessment of gender, race, ethnicity, and other sociodemographic variables. Due to the genetic analysis that are part of this study, we will ask detailed questions about ancestry. To be eligible, a participant must report being predominantly European or African American ancestry. The participant will self-report the race of their parents and grandparents to ensure this criteria is met. In rare cases in which the race of a participant's parents and grandparents are unclear from the participant's self-report, we will conduct genotype analysis of the ancestral marker panel before randomization. Specifically, to be eligible, a participant must be equal or more than 75% of European or African ancestry proportions as determined by a 24-marker ancestry panel.

5. The Slosson Oral Reading Test (SORT-R3) (Slosson Publications, Inc. (unknown) (SORT-R3) Slosson oral reading test, revised preschool-adult. Retrieved on November 8, 2011 from http://www.slosson.com/onlinecatalogstore_c51705.html) - The Slosson Oral Reading Test (SORT) is designed to assess a participant's "level of oral word recognition, word calling or reading level." It is a "quick screening test to determine a student's reading level."

6. Vital signs, weight, height – summarized on the Vital Signs Form.

7. Physical exam – summarized on the Physical Health and Lab Form

8. Medical and psychiatric history – summarized on the Physical Health and Lab Form

9. 12-lead EKG – summarized on Electrocardiogram Results Form

10. Structured Clinical Interview for DSM 5 (SCID; American Psychiatric Association, 2013) - The SCID is a structured diagnostic interview to determine presence of AUD, PTSD, and other psychiatric diagnoses. The SCID will be used to determine study eligibility. The SCID interviews will be audio recorded for training and supervision purposes and to monitor reliability of administration.

11. Life Events Checklist 5 (Weathers, F.W., Blake, D.D., Schnurr, P.P., Kaloupek, D.G., Marx, B.P., & Keane, T.M. (2013). The Life Events Checklist for DSM-5 (LEC-5). Instrument available from the National Center for PTSD at www.ptsd.va.gov) - The Life Events Checklist for DSM-5 (LEC-5) is a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime. The LEC-5 assesses exposure to 16 events known to potentially result in PTSD or distress and includes one additional item assessing any other extraordinarily stressful event not captured in the first 16 items. The LEC was developed concurrently with the Clinician-Administered

PTSD Scale (CAPS) to be administered before the CAPS to establish the presence of a Criterion A trauma which is required for a PTSD diagnosis.

12. Clinician Administered PTSD Scale (CAPS) (Weathers, F.W., Blake, D.D., Schnurr, P.P., Kaloupek, D.G., Marx, B.P., & Keane, T.M. (2013). The Clinician Administered PTSD Scale for DSM-5 (CAPS-5). Interview available from the National Center for PTSD at www.ptsd.va.gov) – Developed by the National Center for PTSD, the CAPS is the gold standard diagnostic assessment for PTSD. The CAPS-5 is a 30-item structured interview that can be used to: make current (past month) diagnosis of PTSD, make lifetime diagnosis of PTSD, and assess PTSD symptoms over the past week. Questions also target the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS administration, overall response validity, overall PTSD severity, and specifications for the dissociative subtype (depersonalization and derealization). For each symptom, standardized questions and probes are provided. Administration requires identification of an index traumatic event to serve as the basis for symptom inquiry. The CAPS interviews will be audio recorded for training and supervision purposes and to monitor reliability of administration.

13. PTSD Checklist (PCL) (Weathers, F.W., Litz, B.T., Keane, T.M., Palmieri, P.A., Marx, B.P., & Schnurr, P.P. (2013). The PTSD Checklist for DSM-5 (PCL-5). Scaleavailable from the National Center for PTSD at www.ptsd.va.gov) - The PCL-5 is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. The PCL-5 has a variety of purposes, including: monitoring symptom change during and after treatment, screening individuals for PTSD, making a provisional PTSD diagnosis. IN this study, the PCL will be used to assess symptoms of PTSD at each study visit.

14. Timeline Follow-Back (TLFB) (Sobell, L.C. & Sobell, M.B. (1992). Timeline Follow-back: A technique for assessing self-reported alcohol consumption. In J. Allen & R.Z. Litten (Eds.), Measuring Alcohol Consumption: Psychosocial and Biological Methods (pp. 41-72). Totowa, NJ: Humana Press) - The TLFB is a daily calendar for alcohol (and other psychoactive substance) consumption that employs memory aids, such as a calendar, to help subjects provide retrospective estimates of their daily drinking as the number of standard drinks for each day. A day is defined as a 24-hour period starting at 6.00 a.m. and ending at 6.00 a.m. the following morning. A month is a period of 28 consecutive days. The TLFB can be completed in a reasonable length of time (approximately 10-15 min) and has been used extensively in pharmacotherapy trials for AUD. At the Screening visit, the TLFB will be used to measure alcohol consumption, and tobacco and cannabis use, for the prior month, or however long is necessary to accurately assess the participant's typical drinking pattern. This information, along with the SCID scale for AUD, will be used in determining the participant's eligibility for the study. At the Baseline visit, the TLFB will be used to measure alcohol consumption, and tobacco and cannabis use for the prior 28 days. At each subsequent visit, the TLFB will be used to measure alcohol consumption, and tobacco and cannabis use, since the prior visit. If the participant misses a scheduled visit and returns for a later visit, the TLFB will be administered to document alcohol consumption during the missed period. For example, if the participant attends Visit 6, does not attend Visit 7, and returns to the study center for Visit 8, the TLFB administered at Visit 8 will elicit consumption data for the period of time since the Visit 6 TLFB administration.

15. Blood collection:

15a. approximately 21 ml (approximately 4 teaspoons) peripheral venous blood for hematology and clinical chemistry tests and DNA extraction and genotyping. Results summarized on the Physical Health and Lab Form.

15b. approximately 25.5 ml (approximately 6 teaspoons) peripheral venous blood for gamma-glutamyl transferase (%GGT) and carbohydrate-deficient transferrin (%dCDT) to assess for the validity of self-report drinking, and for RNA and miRNA for expression studies (to be stored at -80degreesC for future studies). Results summarized on the Physical Health and Lab Form.

16. Urine collection: urine toxicology (presence of psychoactive drugs), urinalysis, and urine pregnancy test (for women of child bearing potential). Results summarized on the Urinalysis Form.

17. Review of other somatic and psychiatric medications - results summarized on Other Medications Form.

18. Suicide Risk Assessment - This is a brief assessment that screens for common risk factors for suicide. This will be completed after administration of the SCID and CAPS. If the estimate of risk is rated as high by the assessor, he/she will engage the participant in a discussion guided by the Suicide Risk Assessment Card to gather more information. If after this discussion the participant's rating is still high, the assessor will contact a health care provider to further evaluate the participant. If the participant is deemed a high risk for current suicidal behavior, he/she will not be entered into the study and will be provided with contact for further treatment including (911 and local ER numbers, crisis hotline numbers). A range of other steps can be taken depending on the assessment of the senior staff member (provide education on warning signs and when further action would be needed, advise to limit access to means of violence, write a safety plan, call a family member or friend, contact a health care provider). If the participant is deemed an imminent risk, the research team will call 911 for transport to St. Agnes Hospital.

19. Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). We will measure depression symptoms with the HAM-D (a 17-item self-report measure) and anxiety symptoms with the HAM-A (a 14-item self-report measure). Eight HAM-D items are rated on a 5-point scale, ranging from 0 = not present to 4 = severe. Nine HAM-D items are scored from 0-2. Items are added to yield a total score; HAM-D total scores are interpreted as follows: 0-7=no symptoms of depression, 8-13=mild symptoms of depression, 14-18=moderate symptoms of depression, 19-22=severe symptoms of depression, >23=very severe symptoms of depression. All HAM-A items are rated on a 0-4 scale; items are added to yield a total score. Total scores are interpreted as follows: 14-17=mild symptoms of anxiety, 18-24=moderate symptoms of anxiety, 25-30=severe symptoms of anxiety.

20. Alcohol Use Disorders Identification Test (AUDIT) (World Health Organization (2001) . The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems. Patients should be encouraged to answer the AUDIT questions in terms of standard drinks. A score of 8 or more is considered to indicate hazardous or harmful alcohol use. The AUDIT has been validated across genders and in a wide range of racial/ethnic groups and is well suited for use in primary care settings.

21. Fagerström Test for Nicotine Dependence (FTND) (Heatherton, et al., (1991).The Fagerström Test for Nicotine Dependence is a standard instrument for assessing the intensity of physical addiction to nicotine. The test was designed to provide an ordinal measure of nicotine dependence related to cigarette smoking. It contains six items that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence. We have also included questions to ask about e-cigarette usage adapted from a recent publication (Johnson et al. Elevated Nicotine Dependence Scores among Electronic Cigarette Users at an Electronic Cigarette Convention. J Community Health (2018) 43: 164-174).

22. Cannabis Use Disorder Identification Test-Revised (CUDIT-R) (Adamson SJ, Kay-Lambkin FJ, Baker AL, Lewin TJ, Thornton L, Kelly BJ, and Sellman JD. (2010). The Cannabis Use Disorders Identification Test–Revised (CUDIT-R) is a brief, eight item screening measure based on the AUDIT, adapted for assessing cannabis use.

23. Pittsburgh Sleep Quality Index (PSQI) (Buysse,D.J., Reynolds,C.F., Monk,T.H., Berman,S.R., & Kupfer,D.J. (1989). The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Research, 28(2), 193-213.) - The PSQI is a self-rated questionnaire assessing sleep quality and disturbances during a 1-month period. It contains 19 items that generate 7 component scores on subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction, all of which add up to a global score. Because sleep disturbance is common in alcoholism, recovery may be associated with improved sleep.

24. The "Religious Background and Behaviors (RBB)" questionnaire is a self-report measure that evaluates the participant's level of religious observance.

25. The "REAPS (Rapid Eating Assessment for Participants - Shortened Version) and "Mediterranean Eating Pattern for Americans" questionnaires are related self-report measures that ask about participants' diets and eating behavior.

26. Stool samples will be collected in order to measure various aspects of the gut microbiome and metabolomics (e.g., biodiversity, butyrate, acetate, and propionate levels, etc.). This is an optional study procedure. Participants who indicate their interest in participating will be provided a stool collection kit to take home, given instructions for collecting the sample at home, and will be instructed to bring the sample back to the lab at their next visit. If they are determined to not be eligible for the study, they will be asked to return to the lab to drop off the sample.

Participants will be monitored for the occurrence of adverse events from the date that the informed consent is signed.
The screening can be done in one or more visits depending on the participant's availability and convenience. If necessary, because of technical issues preventing a valid test or for clinical considerations, we will allow repeating any screening clinical laboratory test at least twice (at the same or future visit).

No assessments will be performed at any subsequent visit unless participants have a BrAC of 0.02% or less. If the participant attends the clinic and has a BrAC greater than 0.02%, the study staff will encourage the participant to wait in the clinic for a sufficient time to permit testing. If a participant records a BrAC > legal definition of intoxication, s/he will be advised to wait until the level falls below the legal level. If the participant insists on leaving with a BrAC that is at or above the legal level, this will be documented in the appropriate section of the CRF. The research team will make a reasonable effort to reach the participant after s/he leaves the clinic to ascertain his/her safety and to encourage him/her to attend the next clinic visit.

If following the in-person screening visit it is determined that an individual meets all eligibility criteria, he/she will be randomized to study condition. The IDS Pharmacy holds the randomization schedule. The study team will provide the necessary information to the IDS Pharmacy for randomization. Specifically, Co-Investigator Dr. Seneviratne determines the genotype and then provides this information to the pharmacy, along with gender, methadone status (yes/no), and depression/anxiety symptoms (High or low). This procedure ensures that all raters, investigators, and other staff are blind to treatment assignments except for the dispensing pharmacist.

The UM Investigational Drug Service (IDS) will provide medication for all study participants, including those who are recruited at the VAMHCS.

III. Baseline Visit (Visit 1)

Participants who have one of the specific desired genotype combinations will be notified of that fact within approximately one week and asked to return within approximately 30 days from screening for the baseline visit. At the baseline visit, the participant will be informed of the randomization and will receive the first dose of pregabalin or placebo based on their assigned randomization schedule. The baseline visit can be spread out over 2 visits, depending on participants' availability and convenience. The baseline visit will consist of the following:

1. BrAC, vital signs, weight, height – summarized on the Vital Signs Form.

2. Urine collection (summarized on the Urinalysis Form) to:

2a test for pregnancy(for women of child-bearing potential).

2b. test for absence of pregabalin. 15 ml of urine will be collected. This test is subsequently used as a verification test for pill taking and a surrogate marker of actual concentrations of the drug in plasma/serum to adjust for individual variations.)

3. TLFB

4. PCL

5. PSQI

6. Clinical Institutes Withdrawal Assessment for Alcohol (CIWA-Ar) (Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989 Nov;84(11):1353-7.) - The CIWA-Ar consists of 10 items, 9 of which (nausea and vomiting, tremor, paroxysmal sweats, anxiety, agitation, tactile disturbances, auditory disturbances, visual disturbances, headache, fullness in head) are rated on a scale of from 0 to 7. The 10th item (orientation and clouding of sensorium) is rated on a scale of from 0-4. It takes approximately 2 minutes to administer and score the CIWA-Ar. The CIWA-Ar scale will be administered by the investigator or another qualified member of the research team. The research team member who administers the CIWA-Ar assessment will be trained in the scoring conventions for the scale.

7. Obsessive Compulsive Drinking Scale (OCDS) (Anton RF, Moak DH, Latham P. The Obsessive Compulsive Drinking Scale: A self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. Alcohol Clin Exp Res 1995;19(1):92-99.) - The OCDS is a 14-item, self-administered questionnaire for characterizing and quantifying the obsessive and compulsive cognitive aspects of craving and heavy (alcoholic) drinking, such as drinking-related thoughts, urges to drink, and the ability to resist those thoughts and urges. It has sensitivity as a monitoring tool and has predictive validity for relapse drinking. Preliminary data also indicate that the OCDS may be a useful screening instrument for the presence of AUD, and may be used to differentiate between individuals with AUD and those who do not drink excessively.

8. Patient Health Questionnaire 9 (PHQ 9; Spitzer RL, Kroenke K, Williams JB (1999). Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. JAMA. Nov 10;282(18):1737–44) - The PHQ-9 is The PHQ-9 is a brief self-report tool that is used to screen for symptoms of depression. It incorporates DSM depression diagnostic criteria into 9 items, each of which are scored on a scale of 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The PHQ-9 will be administered at every study visit. At screening/baseline, participants with severe, untreated depression or who endorse suicidal intent will be excluded from the study and referred for treatment or immediate intervention. At each post-baseline visit, the staff will review the findings on the PHQ-9 to ensure that the participant's safety is not compromised by changes in depression symptoms.

9. Addiction Severity Index - Lite (McLellan AT, Luborsky L, Woody GE, O'Brien CP (1980). An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. Journal of Nervous and Mental Disorders, 168 (1):26-33.)- The Addiction Severity Index, Lite version (ASI-Lite) is a shortened version of the Addiction Severity Index (ASI). The ASI is a semi-structured instrument used in face-to-face interviews conducted by clinicians, researchers, or trained technicians. The ASI covers the following areas: medical, employment/support, drug and alcohol use, legal, family/social, and psychiatric. The ASI obtains lifetime information about problem behaviors, as well as problems within the previous 30 days. The ASI-Lite contains 22 fewer questions than the ASI and omits items relating to severity ratings, and a family history grid.

10. Short Index of Problems (SIP) (Blanchard K; Morgenstern J; Morgan TJ; Labouvie EW; Bux DA. Assessing consequences of substance use: Psychometric properties of the Inventory of Drug Use Consequences. Psychol Addict Behav 2003;17(4):328-331 [though the article title says it is about the InDUC, it is also about the development of the SIP-AD) - The Drinker Inventory of Consequences (DrInC) measures overall consequences of drinking and yields five subscale scores. A short form of the DrInC, the Short Index of Problems (SIP), was developed for use when time does not permit completion of the DrInC. The SIP is a 15-item self-report instrument that measures specific and direct harmful consequences of drinking. Each item is assessed on a 3-point scale ranging from "never or once or a few times" to "daily or almost every day." A lower score indicates fewer adverse consequences of drinking.

11. Clinical Global Impression Scales (CGI-S and CGI-I) (Guy W (ed) (1976) ECDEU assessment manual for psychopharmacology. US Department of Health, Education, and Welfare, Rockville, MD) - The clinical global impression (CGI) rating scales are commonly used clinician-rated measures of global symptom severity and treatment response for patients with mental disorders. Many researchers, while recognizing the validity of the scales, consider them to be subjective as they require the clinician to compare the participants under examination to typical patients from their clinical experience. The Clinical Global Impression – Severity scale (CGI-S) is a seven-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating. Ratings: 1 = Normal, not at all ill, 2 = Borderline mentally ill, 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, 7 = Extremely ill. The Clinical Global Impression – Improvement scale (CGI-I) is a seven-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. Ratings: 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, 7 = Very much worse.

12. WHO DAS (http://www.who.int/classifications/icf/more_whodas/en/) - A global functioning measure developed by the World Health Organization. It can be used across all diseases, including mental, neurological, and addictive disorders. It is short, simple, and easy to administer (5 to 20 minutes), and applicable in both clinical and general population settings. It covers 6 Domains of Functioning, including: Cognition – understanding & communicating, Mobility– moving & getting around, Self-care– hygiene, dressing, eating & staying alone, Getting along– interacting with other people, Life activities– domestic responsibilities, leisure, work & school, Participation– joining in community activities

13. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LESQ) (Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: A New Measure. Psychopharmacology Bulletin 1993;29:321-326.) - a brief measure of quality of life.

14. Review of medication changes and treatment history since screening – summarized on the Other Medications Review Form.

16. Administration of study medication. Study medication will be started in Visit 1. Participants will start at the FDA-recommended initial dose of 150 mg/day and be titrated over 1-3 weeks to a maximum dose of 450 mg/day taken as one pill twice per day. Participants will be tapered off pregabalin over one week, as recommended in the Lyrica® package insert. Dispensing information is summarized on Pregabalin Dispensing Record.

17. Brief Behavioral Compliance and Engagement Training (BBCET) Session 1 (including the SAFTEE for assessment of adverse events; Johnson BA, Ait-Daoud N, Roache JD. The COMBINE SAFTEE: a structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field. J Stud Alcohol Suppl. 2005 Jul;(15):157-67; discussion 140. PubMed PMID: 16223067).

If an abnormality is found during the baseline visit that could pose a risk to the participant, prevent the participant from completing study procedures, or interfere with study results, the investigator may decide not to administer study medication.

Once it has been determined that the participant meets all inclusion and no exclusion criteria, the study medical provider will administer the first dose of study medication and dispense the first week of medication to the participant, giving instructions on how to take the medication twice daily for 12 weeks. The study staff will instruct the participant to call at any time to discuss any problems or concerns that they may have while taking the study medication.

At the end of this visit, study staff will provide instructions about how to participate in remote visits easily and safely. We will strongly encourage the participant to choose a confidential location for these questionnaires. Participants will also be given assistance with using their mobile device or computer for secure video chat via Zoom for Remote Treatment Visits (see below).

Participants will also be instructed to call the study staff at any time even when participating remotely (and on days that no study visits are scheduled) to discuss problems or concerns that they may have while participating in the study. They will be provided with phone numbers to contact the study staff during office hours and a pager number for off-hours contact.

IV. On-treatment visits (Visits 2-11)

Participation will take place every week (+/- 6 days) for 12 weeks. Visits 3, 5, 6, and 9 will occur in-person at an approved study site (referred to below as “In-Person Treatment Visits”), while Visits 2, 4, 7, 8, 10, and 11 will occur remotely by phone or secure Zoom video chat (referred to below as “Remote Treatment Visits”). At each in-person visit, an appropriate amount and doses of study medication will be dispensed so the participant has enough to last until the next in-person visit. All participants who are randomized will be taught the correct use of the study medication which is reviewed at each study visit.

For Remote Treatment Visits, all self-report measures will be administered by a study staff member.

The following list identifies the measures that will be completed during the treatment phase of the study, and at which visits they will be completed:

1. BrAC, body weight, and vital signs (In-Person Treatment Visits) – summarized on the Vital Signs Form.

2. TLFB (All Visits)

3. PCL (All Visits)

4. CIWA-Ar (All Visits) – items that refer to clinical judgment based on participants’ physical appearance/demeanor will be omitted for Remote Treatment Visits)

5. Blood collection (results summarized on the Physical Health and Lab Form):

5a. Blood collection Visits 3 and 9: approximately 11.5 ml (approximately 2 teaspoons) per visit for RNA and miRNA for expression studies (to be stored at -80degreesC for future studies). We will use 0.5-1ml of collected plasma samples to measure plasma/serum pregabalin levels (to perform statistical analyses to test (1) validity of urine pregabalin levels as a surrogate biomarker of plasma/serum levels, and (2) associations with genomic data).

5b. Blood collection Visit 6: approximately 28.5 ml (approximately 6 teaspoons) for gamma-glutamyl transferase (%GGT) and carbohydrate-deficient transferrin (%dCDT) to assess for the validity of self-report of drinking and for RNA and miRNA for expression studies (to be stored at -80degreesC for future studies). We will use 0.5-1ml of this collected plasma sample to measure plasma/serum pregabalin levels (to perform statistical analyses to test (1) validity of urine pregabalin levels as a surrogate biomarker of plasma/serum levels, and (2) associations with genomic data).

6. Urine collection (summarized on the Urinalysis Form) to:

6a. screen for drugs of abuse (Visit 6)

6b. test for pregnancy test (for women of childbearing potential (Visit 6)

6c. test for pregabalin. 15 ml of urine collected to test for pregabalin (as a verification test for pill taking and a surrogate marker of actual concentrations of the drug in plasma/serum to adjust for individual variations) (In-Person Treatment Visits)

7. OCDS (All Visits)

8. PSQI (All Visits)

9. PHQ-9 (All Visits)

10. ASI Lite (Visit 6)

11. SIP (Visit 6)

12. CGI-s and CGI-C (Visit 6)

13. WHO DAS (Visit 6)

14. Q-LESQ (Visit 6)

15. BBCET Sessions (All Visits) (including the SAFTEE for assessment of adverse events)

16. Dispensing study drug (In-Person Treatment Visits)

17. Tracking compliance (In-Person Treatment Visits) - summarized on Pregabalin Dispensing Record

18. Tracking use of other medications (All Visits) – summarized on the Other Medications Review Form.

19. Monitoring of suicidal ideation and behavior (All Visits, as needed) - At all visits, participants will complete the Participant Health Questionnaire 9, a 9-item assessment of depressive symptoms that asks how many days in the last two weeks the respondent experienced different symptoms including thoughts of death and

suicide. A positive response (3+ days or more of suicidal ideation) would lead to the study assessor to engage the participant in a discussion guided by the Suicide Risk Assessment Card to gather more information. If after this discussion the assessor believes the thoughts of suicide are significant, the assessor will contact a health care provider to further evaluate the participant and can utilize a range of other steps depending on the assessment of the senior staff member (provide education on warning signs and when further action would be needed, advise to limit access to means of violence, write a safety plan, call a family member or friend, contact a health care provider). If the participant is deemed a high risk of current suicidal behavior, he/she will be provided with contact for further treatment including (911 and local ER and crisis hotline numbers). If the participant is deemed an imminent risk, the research team will call 911 for transport to St. Agnes Hospital.

For Remote Visits, a different set of procedures will be followed:

1. The study team members will assess the participant further to determine whether intent to harm self and plan to harm self exist.

2. After this assessment, if the study team member's opinion is that the risk of harm is low (no plan, no intent, no means), then he/she will continue with the meeting as planned. At the end of the call, the study team member will advise the participant to talk with his/her outpatient mental health provider soon and will assist as needed in setting up an outpatient appointment.

3. After this assessment, if the staff member's opinion is that there is an elevated risk of harm (maybe plan, maybe intent, maybe means), then he/she will do the following:

a. Notify the PI or one of the co-Investigators.

b. Work with the participant to contact his/her emergency contact (identified on the Subject Locator Form) and ask this contact to go to the participant's location. The plan can be either that the participant calls the contact or that a study team member makes the call. In either case, the study team member will call the participant back to make sure the plan has been implemented and to problem solve if needed (i.e. identify another person who can come to the participant's location).

c. If there is no contact person available and the study staff member believes a threat for self-harm exists, the study staff member will refer the participant to urgent care [i.e. their nearest emergency room] or contact the local crisis response hotline and/or local police (i.e. 911) to evaluate the participant emergently.

20. HAM-D and HAM-A - Visit 6

21. AUDIT - Visit 6

22. CAPS (Visits 5 and 9)

If a participant stops study medication at any time during the study, he/she will be encouraged to continue to attend study visits and participate in all non-study-drug-related procedures.

Emergency unblinding information for each participant will be kept in a locked cabinet at the IDS Pharmacy in the case of a medical emergency. In the event that unblinding is needed, the study physician will call the IDS pharmacy and the pharmacist will inform him of the participant's condition.

V. End of Treatment visit (Visit 12)

1. BrAC, body weight, and vital signs – summarized on the Vital Signs Form.

2. TLFB

3. PCL

4. CIWA-Ar

5. Blood collection - 32.5 ml (approximately 6 teaspoons) peripheral venous blood for hematology and clinical chemistry tests, to determine pregabalin levels, for gamma-glutamyl transferase (%GGT) and carbohydrate-deficient transferrin (%dCDT) to assess for the validity of self-report drinking, and for RNA and miRNA for expression studies (to be stored at -80degreesC for future studies). We will use 0.5-1ml of this collected plasma sample to measure plasma/serum pregabalin levels (to perform statistical analyses to test (1) validity of urine pregabalin levels as a surrogate biomarker of plasma/serum levels, and (2) associations with genomic data). Results will be summarized on the Physical Health and Lab Form.

6. Urine collection to screen for drugs of abuse, test for pregnancy (for women of childbearing potential), and test for pregabalin (15 ml of urine collected as a verification test for pill taking and a surrogate marker of actual concentrations of the drug in plasma/serum to adjust for individual variations) – summarized on the Urinalysis Form.

7. OCDS

8. PSQI

9. PHQ-9

10. ASI Lite

11. SIP

12. CGI-s and CGI-C

13. WHO DAS

14. Q-LESQ

15. AUDIT

16. BBCET – Final Session (including the SAFTEE for assessment of adverse events)

17. HAM-D and HAM-A

18. CAPS

19. Tracking compliance - summarized on Pregabalin Dispensing Record

20. Tracking use of other medications – summarized on the Other Medications Review Form.

As noted above, we conduct urine pregnancy tests and urine drug screening at the In-person screen (both), Visit 1 (pregnancy test only) Visit 6 (both), and Visit 12 (both). At the discretion of the study team, we will collect additional pregnancy tests and drug urine tests at any study visit if needed, for example, in cases where a participant's self-report of use of contraception or other drug use may be unreliable (e.g., the participant gives one set of information to a study clinician and differing information to another study team member) or for any reason related to the study team's belief that it is in the best interest of participant safety.

VI. Safety Follow-up Phone Call (Week 13)

At week 13, research staff will call the participant to assess the experience of persistent adverse events following the cessation of study medication.

VII. Other Policies and Procedures

COVID-19-related Policies. Due to the ongoing COVID-19 pandemic, all participants scheduled to complete any in-person study participation at UMB must complete a COVID-19 symptom and exposure screening prior to confirming their attendance one business day before the scheduled appointment. This questionnaire is used to assess symptoms of and likelihood of exposure to the virus. If the participant indicates that they have any of the common symptoms (i.e., fever, cough, shortness of breath), if they have been in close contact with anyone who has tested positive for COVID-19 or are awaiting results, or if they or someone in their household have cared for someone in quarantine or presumed positive for COVID-19, they will not be permitted to attend the study visit. Additional consideration for attending in-person study visits will be given if a participant indicates any of the following: they or someone in their household have recently visited a hospital, nursing home, or long-term care facility; they attended a large gathering with inadequate physical distancing and/or mask-wearing; they have recently been tested for COVID-19 or believe they should be; or if they have traveled outside of the State of Maryland. Research assistants conducting this screening will communicate with a clinician to approve any questionable symptoms or exposure.

The day of the scheduled appointment, the questionnaire will be repeated again before the participant travels to the study site. Upon arrival, the participant's temperature will be taken and must be below 101 degrees F to proceed into the building.

The screening questionnaire will be completed 3-4 days following study participation to ensure that symptoms have not developed since attending the visit. If any are reported, the study PI will be notified and the participant will consult with a clinician to ensure the appropriate steps are taken in the interest of public health and contact tracing.

RESCHEDULING STUDY VISITS. If a participant informs the study staff ahead of time that they will miss an In-Person Treatment Visit (e.g., due to a vacation), they will be provided with enough study medication to ensure the maintenance of the daily dosage of study medication until the next scheduled visit as per the dosing schedule.

In emergency scenarios (e.g., the COVID-19 pandemic), we may need to deliver medication to active participants via mail. We will work with the IDS pharmacy to ensure that the procedure for shipping medication follows United States Postal Service (USPS) guidelines. The USPS regulations permit the mailing of any controlled substance, provided it is not outwardly dangerous and will not cause injury to a person's life or health, and if the following preparation and packaging standards are met:

*The inner container of any parcel containing controlled substances is marked and sealed as required by the provisions of the CSA and its implementing regulations, and is placed in a plain outer container or securely wrapped in plain paper.
*If the controlled substance consists of prescription medicines, the inner container is also labeled to show the name and address of the pharmacy, practitioner, or other person dispensing the prescription.
*The outside wrapper or container is free of markings that would indicate the nature of the content.

IDS uses overnight FedEx service for shipping medication. If medication needs to be shipped from IDS to the participant, we will notify the participant on the day that the package is set to arrive and then ask that they confirm when they have picked it up. We will follow up with the participant over the phone to confirm the correct medication has been received and provide instructions for taking the medication. If the participant is unable to return to in-person study participation before the end of the study, they will be able to ship their unused medication back to IDS via a pre-paid FedEx shipping container.

For UM participants, study visits will occur at either the Maryland Psychiatric Research Center (MPRC) at 55 Wade Avenue or the University of Maryland Medical Center General Clinical Research Center (UMMC GCRC). For visits that take place at the MPRC, transportation will be provided (if needed) from the participant's home to the center and back. If the participant prefers, he/she can arrange his/her own transportation. For visits that that place at the UMMC GCRC, the participant can arrange his/her own transportation and be met at the hospital, or can request assistance with transportation if needed.

2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):

N/A

3 * Describe the duration of an individual participant's participation in the study:

Telephone Screening
In-person Screening
Visit 1 = In-person - Baseline + randomization + treatment session 1 + medication starting dose
Visit 2 = Remote - treatment session 2 + medication uptitration
Visit 3 = In-person - treatment session 3 + medication uptitration
Visit 4 = Remote - treatment session 4 + medication uptitration
Visit 5 = In-person - treatment session 5 + medication maintenance
Visit 6 = In-person - treatment session 6 + medication maintenance
Visit 7 = Remote - treatment session 7 + medication maintenance
Visit 8 = Remote - treatment session 8 + medication maintenance
Visit 9 = In-person - treatment session 9 + medication maintenance
Visit 10 = Remote - treatment session 10 + medication downtitration
Visit 11 = Remote - treatment session 11 + medication downtitration
Visit 12 = In-person - treatment session 12 (no medication)
Visit 13 = Remote – follow-up telephone call (approximately 1 week after last visit)
Total = Approximately 14 weeks

4 * Describe the amount of time it will take to complete the entire study:

Approximately 5 years to complete

5 * Describe any additional participant requirements:

None

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Provide the rationale and sample size calculations for the proposed target population:

We calculated sample size for a Cohen's d effect size equal to 0.31 (at week 12) based on prior studies of Pregabalin for PTSD (Baniasadi et al., 2014) and AUD (Martinotti et al., 2010). We assumed cumulative attrition equal to 25% and correlation among repeated measures equal to 0.55. With a power = 0.80 and alpha-level = .05/2 = .025 (i.e., corrected for two main effect hypotheses), the required sample size is N = 198. The online RMASS (Repeated Measures and Sample Size) calculator based partly on Hedecker (1999) was used to perform the calculation.

2 * Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:

Analysis Population: All randomized AUD/PTSD African-American participants who received at least one dose of medication. NOTE: This means that we will NOT test Specific Aim 3 – there were not enough European Americans recruited into the sample to conduct a comparison by race.

A. Describe the sample
Variables/measures we will use to describe the sample are:
- Demographics: age, sex/gender, education, SES (income and employment), collected at screening
- Life events checklist, collected at screening
- PCL, collected at screening
- CAPS, collected at screening
- TLFB30 drinks per week (DPW), drinks per drinking day (DPDD), heavy drinking days (HDD); collected at screening
- OCDS, collected at baseline
- CIWA, collected at baseline
- AUD severity defined as a symptom count from the SCID
- Smoking status defined as smoking >= 10 cigarettes in past 90 days from the "Other Drug Use" form
- Vital signs: BMI calculated from height and weight, collected at screen

B. Specific Aim 1 (SA1): To test the hypothesis that African American AUD/PTSD participants treated with pregabalin will demonstrate a greater reduction in heavy drinking than African American placebo treated participants.

Primary outcome: HDD during the past 7 days assessed weekly during treatment with the TLFB. NOTE: We will adjust for drinking last 30 days at screening.

Secondary outcomes:
- DPW and DPDD during the past 7 days assessed weekly during treatment with the TLFB.
- Number of days abstinent (NDA) during the past 7 days assessed weekly during treatment with the TLFB. NOTE: We will adjust for drinking last 30 days at screening.
- %dCDT measured via blood samples collected at screening, midpoint (Visit 6), and end-of-study (Visit 12).
- GGTP measured via blood samples collected at screening, midpoint (Visit 6), and end-of-study (Visit 12).

SA1 Analysis: For HDD and secondary TLFB outcomes, a repeated measures mixed effects model will be used to compare change over the twelve weekly assessments between the two treatment conditions. The model will be a generalized linear or linear model depending on the distribution of the outcome. A quadratic term for time will be specified to capture non-linear change. To reduce residual error and maximize power, we will adjust for a pre-baseline assessment of the outcome. Overall, the regression model will be:

Outcome = pre-baseline Outcome + txgroup + week + week2 + week□txgroup + week2□txgroup

The analysis model for %dCDT of and GGTP will assess the time-averaged (over visits 6 and 12) difference between treatment groups adjusting for baseline. The model will account for within-individual correlations with a random effect for participant.

C. Specific Aim 2 (SA2): To test the hypothesis that African American AUD/PTSD participants treated with pregabalin will demonstrate a greater reduction in PTSD cluster B or E symptoms (or both) than African American placebo-treated participants.

Primary outcomes:
- PCL cluster B symptom severity scores, assessed weekly during treatment.
- PCL cluster E symptom severity scores, assessed weekly during treatment.
- NOTE: We will adjust for PCL score collected at screening.

Secondary outcomes:
- PCL total symptom score, assessed weekly during treatment. NOTE: We will adjust for PCL score collected at screening.
- CAPS cluster B and E symptom severity scores, assessed at weeks 4, 8, and 12 during treatment. NOTE: We will adjust for CAPS score collected at screening.

SA2 Analysis: The analysis of the primary outcomes will use the same regression model described for drinking outcomes in SA1. Analysis of the CAPS scores will be a repeated measures mixed effects model to test the difference in the mean across weeks 4, 8, and 12 adjusting for the pre-baseline score.

D. Specific Aim 4 (SA4): To test the hypothesis that the treatment responses to pregabalin in African American AUD/PTSD participants specified in SA1 and SA2 are moderated by genetic variations within SLC6A1 gene.

Analysis: This analysis will examine whether there is a difference of treatment effect between two SLC6A1 gene variant groups, i.e., the non-insertion/insertion or insertion/insertion variant group (NI/I or I/I) versus the non-insertion/non-insertion (NI/NI) variant. A binary indicator will be constructed to indicate the NI/I or I/I versus NI/NI variant. The analysis will be conducted by adding the main effect and interaction terms of this binary indicator to the above regression model to test whether there is a difference in treatment effect by SLC6A1 gene group on the primary outcomes specified in SA1 and SA2.

Sharing of Results

1 * Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared:

Clinically significant abnormalities detected in any diagnostic tests or detected during a physical examination will be discussed with the participant and the participant referred for further evaluation or management by their primary care physician. With the participant's permission, findings will be shared with participant's health care provider.

ID: VIEW4E02808CBD800
Name: v2_Sharing of Results

Research with Drugs or Biologics

You indicated on the "Type of Research" page that your study involves use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol AND/OR evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.

1 * List all drugs/biologics to be administered in this study. Be sure to list each drug/biologic with its generic name only.

	Drug Name	FDA Approved	IND Number	PI IND Holder
View	Pregabalin	yes	N/A	

2 * Attach the drug package insert or investigational drug brochure for the drugs being administered in this study:

LyricaFDAlabel(June2012).pdf(0.01) 8/26/2016 7:19 AM 8/26/2016 7:19 AM

3 If more than one drug is administered, discuss the risk implications of drug/therapy interactions:

4 * Will you be using Investigational Drug Services?

● **Yes** ○ No

ID: VIEW4E0916E6E1400
Name: v2_Research with Drugs or Biologics

Advertising Detail

You indicated that you will be using advertisements to recruit potential participants.

1.1 * Select the mode(s) of advertising (check all that apply):

- [x] **Radio**
- [x] **Internet**
- [x] **Print**
- [ ] Television
- [x] **Other**

1.1.1 If Other, specify:

craigslist
social media
mass transit (e.g., outsides of buses, trains, light rail; posters at transit stops)
Research Match
posting and distributing flyers and ads at health care, educational, and other community sites

1.2 * Provide exact text of all proposed advertisement(s):

WANT TO REDUCE OR STOP YOUR DRINKING?

A 14-week study being conducted by the University of Maryland Department of Psychiatry is testing a medication to help people who have experienced trauma in their lives to reduce or stop drinking. Participants who qualify receive education and study medication (active drug or inactive placebo). Appointments are individual and confidential. All visits, lab work, and study procedures are provided at no cost to you. You will be compensated for your participation.

If you are a regular or daily drinker, age 18 to 65, have experienced trauma in your life, and want to stop or reduce drinking alcohol, contact study staff at:

(410) 402-6412
rethinkyourdrinking@som.umaryland.edu

ALL CALLS ARE CONFIDENTIAL
UMB IRB HP-69465

Have you experienced a traumatic event in your life?
Do thoughts about this experience affect you now?
Do you use alcohol to get relief?

We are conducting a research study of a medication that may help people who have experienced a traumatic event feel better and drink less. Traumatic events are things like physical or sexual assault, war zone exposure, serious accidents, and natural disasters. We are looking for:

- People who are age 18-65
- Males and females
- People in generally good health

Participation is confidential. You will be compensated for your time.
Transportation is available. To learn more, go to:

www.rethinkyourdrinking.org
Or contact us
By phone: (410) 402-6412
By email: rethinkyourdrinking@som.umaryland.edu

All calls are confidential.
UMB IRB HP-69465

1.3 * Upload advertisement(s) here:

Name	Created	Modified Date
Rethink Drinking 30 3_6.mp4(0.01)	4/6/2021 11:27 AM	4/6/2021 11:27 AM
Rethink Drinking 15 3_6.mp4(0.01)	4/6/2021 11:27 AM	4/6/2021 11:27 AM
Pregabalin study_radio ad text_2 9 2021.docx(0.03)	5/29/2019 2:30 PM	2/16/2021 11:52 AM
Pregabalin study_Brief radio and TV ad text_2 9 2021.docx(0.03)	5/29/2019 2:30 PM	2/16/2021 11:51 AM
Pregabalin_Color ad and flyer14_2 9 2021.docx(0.02)	5/29/2019 2:31 PM	2/9/2021 4:49 PM
Pregabalin_Color ad and flyer13_2 9 2021.docx(0.02)	5/29/2019 2:31 PM	2/9/2021 4:49 PM
Pregabalin_Color ad and flyer12_2 9 2021.docx(0.02)	5/29/2019 2:31 PM	2/9/2021 4:48 PM
Pregabalin_Color ad and flyer11_2 9 2021.docx(0.02)	5/29/2019 2:31 PM	2/9/2021 4:48 PM
Pregabalin_Color ad and flyer10_2 9 2021.docx(0.02)	5/29/2019 2:31 PM	2/9/2021 4:48 PM