Topiramate and Prolonged Exposure

NCT03176953

Last Approved/Updated 10/04/2023

Human Protocol (Version 1.49)

General Information

***Please enter the full title of your study::**

Combining Topiramate and Prolonged Exposure for PTSD and Alcohol Use Disorder

***Please enter the Study Number you would like to use to reference the study:**

TOP Study
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

Add departments

and Specify Research Location:

Is Primary?	Department Name
◉	**VASDHS** - VASDHS

Assign key study personnel(KSP) access to the study

***Please add a Principal Investigator for the study:**

Norman, Sonya B., PhD

3.1 If applicable, please select the Research Staff personnel

A) Additional Investigators

Angkaw, Abigail Candare, PhD
Co-Investigator
Brody, Arthur L., MD
Co-Investigator
Davis, Brittany C
Co-Investigator
Lacefield, Katharine I., PhD
Co-Investigator
Martis, Brian, MD
Co-Investigator
Matthews, Scott Christian, MD
Co-Investigator
Pitts, Michelle, PhD
Co-Investigator
Risbrough, Victoria B., PhD
Co-Investigator

Stein, Murray B., MD
Co-Investigator
Townsend, Andrea Spadoni, PhD
Co-Investigator

B) Research Support Staff

Higdon, Alexandra O., PsyD
Research Associate
Holcomb, Julie M.
Clinical Research Associate
Katawazi, Julia G.
Clinical Research Associate
Klein, Alexandra, PhD
Post-Doc
Kline, Alexander C., PhD
Post-Doc
Luciano, Matthew T., PhD
Research Associate
Lyons, Robert C., PhD
Student
Marvin, Morgan E., BA
Research Associate
Miller, Ruth Klaming, PhD
Research Associate
Panza, Kaitlyn E., PhD
Study Coordinator
Park, Jae Eun
Research Associate

***Please add a Study Contact**

Norman, Sonya B., PhD
Panza, Kaitlyn E., PhD

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

VASDHS - IRB Protocol

v20150312

Section 1 - Preliminaries

Principal Investigator:

Sonya B. Norman, PhD

Protocol Title:

Combining Topiramate and Prolonged Exposure for PTSD and Alcohol Use Disorder

IRB Protocol Number:

H170056

Protocol Nickname:

TOP Study

Form Template Version:

v20150115

Date Prepared:

10/04/2023

1a) Is this study considered human research?

(•) Yes ( ) No

1b) Is this a request for a determination of exemption from IRB review?

( ) Yes (•) No

1c) Is this a request for an expedited IRB review?

( ) Yes (•) No

Section 1.3 New Protocol or Transfer/Renewal of Prior Protocol

1.3) Select the type of protocol application:

1.3a) Is this a new protocol? (if transfer to VA IRB, select **No**)

(•) Yes ( ) No

1.3b) Is this a resubmission of a VASDHS IRB protocol?

( ) Yes (•) No

1.3c) Is this a transfer of a protocol to the VASDHS IRB?

( ) Yes (•) No

Section 2 - Research Subjects

2a) What is the total planned number of VASDHS-consented subjects needed?

(Include even if using a waiver of documented consent, e.g. oral consents)

120

2b) What is the total number of VASDHS subjects needed that WILL NOT be consented (e.g., retrospective reviews) ?

0

Section 2.1 Consented Subject Groups

2.1) For each of the subject categories listed below, indicate whether or not these subjects will be enrolled (consented) in the study: (exclude cases of data or specimens only)

2.1a) Children under age 18

○ Yes ◉ No

2.1b) Women of child-bearing potential

◉ Yes ○ No

2.1c) Pregnant women

○ Yes ◉ No

2.1d) Individuals with cognitive/decisional impairment

○ Yes ◉ No

2.1e) Non-English speaking individuals

○ Yes ◉ No

2.1f) Prisoners of War [explicitly targeting this group]

○ Yes ◉ No

2.1g) Non-Veterans (Note: A justification will be required below)

○ Yes ◉ No

2.1h) Incarcerated individuals (Note: VA CRADO approval will be required)

○ Yes ◉ No

2.1i) VA employees (or WOCs)

○ Yes ◉ No

2.1j) Students

○ Yes ◉ No

2.1k) Patients with cancer (or high cancer risk) [explicitly targeting this group]

○ Yes ◉ No

Section 3 - Study Features (these items default to "No" for convenience)

3) This section consists of several Yes/No questions addressing protocol characteristics. Click on *Save and Continue*.

Section 3.1 Protocol Basics

Indicate whether or not each of the following applies to this protocol

3.1a) The research **intends to change** the participant

◉ Yes ○ No

3.1b) **Interactions** with living participants to collect data or specimens with no intent to change them.

◉ Yes ○ No

3.1c) This is a study that **never** has any **subject contact or subject identifiers** (e.g., de-identified tissue only).

○ Yes ◉ No

3.1d) This is a **multi-site** study (multiple IRB's involved) and **VASDHS** is the **main** or a coordinating site

○ Yes ◉ No

3.1e) This is a **multi-site** study (multiple IRB's involved) and VASDHS is NOT the main or a coordinating site

○ Yes ◉ No

3.1f) There is an **international** component to this research

○ Yes ◉ No

3.1g) Any study activity occurs at **non-VASDHS locations** (not including VHASDC leased space or clinics) under the VASDHS IRB protocol.

○ Yes ◉ No

3.1h) VASDHS subjects **participate** in whole or in part **at other locations** (not including VHASDC leased space or clinics) under this VASDHS IRB protocol.

○ Yes ◉ No

Section 3.2 Specimen Use and Data Repository

Indicate whether or not each of the following applies to this protocol

3.2a) Involves specimens that are left over from pathological or diagnostic testing (**non-research specimens**)

○ Yes ◉ No

3.2b) Involves **specimens collected for research** purposes **only**

◉ Yes ○ No

3.2c) This study includes **specimen banking** (specimens are retained for use outside of the purposes of this protocol)

◉ Yes ○ No

3.2d) The study involves **DNA** genotyping or other **genetic analysis**

◉ Yes ○ No

3.2e) A Biological **Materials Transfer** Agreement is required.

◉ Yes ○ No

3.2f) A **data repository** is maintained (data are retained after completion of the protocol for other uses, IMPORTANT see ? before checking "yes")

◉ Yes ○ No

Section 3.3 Treatment and Clinical Trials

Indicate whether or not each of the following applies to this protocol

3.3a) Includes a **treatment** component (a research treatment)

◉ Yes ○ No

3.3b) Study is a **clinical trial**

(•) Yes ( ) No

3.3c) Has a data safety monitoring board (**DSMB)** or data safety monitoring committee

( ) Yes (•) No

3.3d) Has a **data safety monitoring plan** (but not a DSMB) (this is not the data security plan, it is a safety plan)

(•) Yes ( ) No

Section 3.4 Drugs and Devices

Indicate whether or not each of the following applies to this protocol

3.4a) **Drugs** that require **FDA** action such as an Investigational New Drug (IND) approval or exemption or 510(k) approval.

( ) Yes (•) No

3.4b) Other drugs that **do not require FDA** action for inclusion in the study

(•) Yes ( ) No

3.4c) Medical **devices requiring FDA** IDE approval or waiver

( ) Yes (•) No

3.4d) **Other** medical **devices**

( ) Yes (•) No

Section 3.5 Risk and Hazards

Indicate whether or not each of the following applies to this protocol

3.5a) Study places subjects at **greater than minimal risk** (do not include risks that are due to standard care)

(•) Yes ( ) No

3.5b) Human subjects are exposed to **radioisotopes** (do not include standard care)

( ) Yes (•) No

3.5c) Subjects have other **radiation exposure** (e.g., x-rays) (do not include standard clinical use)

( ) Yes (•) No

3.5d) Target population has psychiatric diagnosis or behavioral complaint.

(•) Yes ( ) No

Section 3.6 Clinical Facilities and Standard Care

Indicate whether or not each of the following applies to this protocol

3.6a) Study **uses VA clinical services** (e.g., adds required tests run in the VA lab for study purposes)

(•) Yes ( ) No

3.6b) Includes procedures or drugs that will be considered **part of standard care**

(•) Yes ( ) No

3.6c) Involves **lab tests done for research** purposes

(•) Yes ( ) No

Section 3.7 Subject Expenses and Compensation

Indicate whether or not each of the following applies to this protocol

3.7a) There may be expense or added **costs to the subject** or the subject's insurance.

( ) Yes (•) No

3.7b) This is a **qualifying cancer treatment trial** and subjects may be billed for study drugs or procedures.

( ) Yes (•) No

3.7c) This is a cancer treatment trial but **subjects will not be billed** for study drugs or procedures.

( ) Yes (•) No

3.7d) Subjects will be **compensated** (either in cash or other means such as a gift certificate)?

(•) Yes ( ) No

Section 3.8 Subject Activities

Indicate whether or not each of the following applies to this protocol

3.8a) Involves **surveys or questionnaires** completed by subjects

(•) Yes ( ) No

3.8b) Includes the use of **recruitment materials** such as flyers, advertisements, or letters

(•) Yes ( ) No

3.8c) Involves facial **photographs** or audio or video **recordings** of **patients**

(•) Yes ( ) No

Section 3.9 Sponsors and Collaboration

Indicate whether or not each of the following applies to this protocol

3.9a) This research has a **commercial (industry) sponsor.**

( ) Yes (•) No

3.9b) Other **commercial (industry) non-financial support** is provided (e.g., drugs or supplies).

( ) Yes (•) No

3.9c) The PI or other study staff member has a financial interest or other **real or potential conflict** related to this study.

○ Yes ◉ No

3.9d) The protocol has **Department of Defense** involvement (e.g., subjects or funding).

○ Yes ◉ No

3.9e) **Non-VASDHS Research collaborators** (either researchers or entities, not VA WOCs, can be VA Other service also) are involved in this VASDHS IRB protocol. (Generally they cannot have access to sensitive information)

◉ Yes ○ No

Section 4 - Estimated Duration

4) What is the estimated duration of the entire study? (From IRB approval to IRB closure)

4 years

Section 5 - Lay Language Summary

5) Provide a summary or synopsis of the proposed study using non-technical language (not more than 1 paragraph)

The present study was designed to find out more about how to effectively treat people who are experiencing symptoms related to alcohol disorder (AUD) and posttraumatic stress disorder (PTSD). This study will compare Topiramate vs. placebo (sugar pill) among Veterans who will also concurrently receive prolonged exposure therapy (PE), an evidence based psychotherapy for PTSD.

Section 6 - Specific Aims

6) Provide a statement of specific aims and hypotheses that serve as the basis for this protocol. Emphasize those aspects that justify the use of human subjects.

Alcohol use disorder (AUD) and posttraumatic stress disorder (PTSD) frequently co-occur, and having one condition worsens the course of the other [15, 16]. Individuals with both disorders exhibit worse functioning across a number of domains than individuals with either disorder alone [e.g., 17, 18]. Prolonged exposure therapy [PE; 19] is among the most effective treatments for PTSD [3]. PE has been rated as a frontline treatment by multiple guidelines and reviews including the VA/DoD Clinical Practice Guidelines for the treatment of PTSD [20]. However, among samples with PTSD and AUD, changes in alcohol use following PE are only slightly better than in control or standard care conditions, reductions in PTSD symptoms are modest relative to studies of PE in PTSD patients without AUD, and rates of drop out from treatment are high [8]. Thus, studies of adjunctive treatments, such as medication, are critical to improve the benefits of PE for individuals who have AUD in addition to PTSD [4]; however, few studies have examined combining psychotherapy and medication [4] and none have examined Topiramate (TOP). TOP is the single medication that has shown effectiveness for both AUD and PTSD [3, 5] and shows promise for reducing drinking among individuals with AUD and PTSD [10]. The key next step is to test a best practice PTSD treatment, PE, together with a uniquely promising pharmacological agent, TOP.

The proposed study is designed to extend our prior research to identify effective treatments for comorbid AUD and PTSD with the goals of reducing problematic alcohol use and PTSD symptoms and improving functioning. We propose to use a randomized, controlled, double blind study design to examine the effect of adding TOP to a best practice treatment for PTSD, PE. Participants will be 120 male and female Veterans from all service eras with AUD and PTSD. Our central hypothesis is that PE+TOP will reduce alcohol use, ameliorate PTSD symptoms, and improve functioning and quality of life more than will PE+Placebo (PLA). Thus, there are three

specific aims and additional exploratory aims:

Aim 1: To determine the relative efficacy of PE+TOP, as compared to PE+PLA, in reducing heavy drinking among Veterans with comorbid AUD/PTSD at post-treatment and 3- and 6-month follow-up.

Hypothesis 1. We hypothesize that AUD/PTSD Veterans receiving PE+TOP will have fewer heavy drinking days at post-treatment and 3- and 6-month follow-up after active treatment compared with participants receiving PE+PLA.

Aim 2: To determine the relative efficacy of PE+TOP, as compared to PE+PLA, in reducing PTSD and depression symptoms in Veterans with comorbid AUD/PTSD at post-treatment and 3- and 6-month follow-up.

Hypothesis 2. We hypothesize that those receiving PE+TOP will show greater improvements in PTSD and depression symptoms at post-treatment and 3- and 6-month follow-up compared with participants receiving PE+PLA.

Aim 3: To determine the relative efficacy of PE+TOP, as compared to PE+PLA, in improving functioning and quality of life among Veterans with comorbid AUD/PTSD at post-treatment and 3- and 6-month follow-up.

Hypothesis 3. We hypothesize that AUD/PTSD Veterans receiving PE+TOP will show greater improvements in functional impairment and quality of life at post-treatment and 3- and 6-month follow-up compared with participants receiving PE+PLA.

Exploratory Aims: We will explore 1) the extent to which decreases in drinking and PTSD symptoms are associated with improvements in functioning; 2) whether PE completion and reductions in heavy drinking at post-treatment and follow-up in the PE+TOP condition are partially mediated by reduction in alcohol cravings and PTSD symptoms during the first half of treatment, and 3) whether reductions in cognitive functioning between baseline and mid-treatment will be associated with less PTSD symptom reduction and less reduction in subjective units of distress (SUDs) during imaginal exposure across PE sessions. Additionally, we will look for genetic associations with treatment response.

The proposed study is highly relevant to the goals of RR&D and the VA. It has the potential to improve functional and psychological recovery for a highly prevalent and highly impaired population of Veterans. This efficacy trial will test a novel and innovative combination of psychotherapy and medication with the goal of improving the care of Veterans. The successful completion of this project will help change the practices that drive treatment for Veterans with comorbid AUD and PTSD. The fundamental rationale for this study is to improve the evidence base that informs how patients with AUD and PTSD can attain sustained recovery from both of these disorders.

Section 7 - Background and Significance

7) Provide a succinct discussion of relevant background information to justify performing the proposed study.

Co-Occurring AUD & PTSD Is Associated with Poor Psychological and Functional Outcomes. Comorbidity of AUD and PTSD is high. Up to 28% of women and 52% of men [21] with PTSD meet criteria for AUD, and rates of PTSD among patients with AUD are as high as 30-59% [22, 23]. Furthermore, there is evidence that AUD and PTSD can co-occur at even higher rates among Veterans [18, 24]. In a national sample of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans using VA care, 62% of those with AUD had a diagnosis of PTSD. Alcohol or substance use disorder was associated with a four-fold increase in likelihood of having a PTSD diagnosis [7].

Individuals with AUD/PTSD generally fare worse than those with either disorder alone [16, 25]. While PTSD and AUD are each associated with functional impairment, individuals who have both disorders have poorer treatment outcomes, more additional psychiatric problems, and more functional problems across multiple domains, including medical, legal, financial, and social domains [18], than those with just one disorder [16-18, 26-29]. AUD/PTSD patients who receive PTSD treatment are more likely to reduce their alcohol use and less

likely to relapse to problem drinking than are patients who receive AUD only treatment [30-32].

Prolonged Exposure (PE) therapy is a best practice treatment for PTSD. The theory behind prolonged exposure [PE; 19] posits that exposure to avoided stimuli and emotional processing of avoided trauma memories are necessary for recovery from PTSD. In this model, exposure works through emotional processing changes that occur in tandem with habituation. When applying emotional processing theory to PTSD, Foa and colleagues [19] proposed two dysfunctional cognitions that are related to the development and maintenance of PTSD: 1) The world is completely dangerous; and 2) I am incompetent (i.e., "I am crazy"). Through the process of repeated, prolonged confrontation of trauma-related stimuli, habituation of emotional responses associated with the trauma occurs. As trauma-related stimuli are repeatedly confronted without the occurrence of feared consequences (e.g., "going crazy") and with lessening emotional activation, the patient experiences repeated evidence that disconfirms the dysfunctional cognitions. A stronger sense of self-competence and control over negative affect and stimuli may allow patients to reduce trauma-related avoidance, leading to even more spontaneous exposure and continued reduction of PTSD symptoms and functional recovery [33]. Alcohol becomes less needed to medicate the symptoms of PTSD or cope with associated problems, thus, alcohol treatment can be more effective than when PTSD is not also addressed. The efficacy of PE has been examined in multiple studies with a variety of populations including Veterans [34, 35]. Treatment guidelines such as the VA/DoD Clinical Practice Guidelines for PTSD support exposure therapy as a first line treatment [20, 36]. However, until recently, individuals with AUD were excluded from studies of PE.

PE helps both AUD and PTSD, but symptom reduction in comorbid individuals is modest and dropout is high. AUD/PTSD patients traditionally received sequential treatment with AUD treated first and PTSD second [26, 37, 38]. This older approach was based, in part, on the notion that individuals with AUD could not tolerate trauma-focused treatment and that such treatment would lead to an exacerbation of alcohol use or other unsafe coping mechanisms. However, research does not support such clinical dogma [16] and a temporal study of patients with AUD/PTSD found that improvements in PTSD symptoms had a greater association with reduced drinking than vice versa [16]. A meta-analysis [8] that included 14 studies of psychotherapy for comorbid PTSD and AUD or another substance use disorder (SUD) found that exposure therapy in combination with AUD therapy was effective in reducing the symptoms of PTSD and problem alcohol use. However, while exposure therapies were more effective than other types of therapies for co-occurring PTSD and AUD, effect sizes were small and dropout rates were higher than in non-exposure based treatments. These results highlight the need to identify ways to boost the effects of PE on PTSD for individuals who also have an AUD.

Medications may improve the efficacy of PE for AUD/PTSD. Ralevski and colleagues recently conducted a review of PTSD/AUD treatment studies and noted that the most promising but understudied treatment direction is combining evidence based psychotherapy and medication [4]. They noted that only one trial to date combined evidence based AUD medication with evidence based PTSD psychotherapy (PE). Specifically, Foa and colleagues [39] recently completed a randomized controlled trial (RCT) of PE and naltrexone for the treatment of AUD and PTSD. Participants were randomized to one of four conditions: PE with either naltrexone or placebo, or supportive therapy with either naltrexone or placebo. All four groups had reductions in PTSD symptoms and alcohol use post-treatment. By 6-months post-treatment, all four groups were drinking more, but the group that received PE and naltrexone showed the smallest increase in drinking. While naltrexone (NAL) is an effective and widely studied AUD medicine, for a number of reasons described below, TOP shows even greater promise for improving outcomes of Veterans with AUD/PTSD who receive PE. However, TOP has not yet been studied together with evidence based psychotherapy for PTSD [4].

TOP is the only medication effective in treating both AUD and PTSD. TOP is a sulfamate-substituted fructopyranose derivative approved by the FDA for the treatment of epilepsy, prophylaxis of migraine headaches, and, in combination with phentermine, for obesity. Among its multiple effects, TOP dampens glutamatergic neurotransmission via its antagonistic effects at AMPA/kainate receptors while simultaneously enhancing GABAergic tone through its allosteric effects at GABA-A receptors [40]. This unique mechanism of action impacts dopaminergic neurotransmission in mesocorticolimbic pathways and may diminish the effects of alcohol, thus, rendering drinking less reinforcing. Because TOP is both a glutamate receptor antagonist and also inhibits dopamine release, TOP may be uniquely effective for comorbid AUD/PTSD patients because it acts on drinking and PTSD symptoms through two separate mechanisms. It received the highest recommendation level for the treatment of AUD in the 2015 VA/DoD substance use disorder guidelines [2] and, in regard to PTSD, a recent review concluded it was one of the most promising medications [3] in need of further study. Meta-analyses examining its effects as a treatment for alcohol use disorder [5, 41] and PTSD [3], respectively, have found the medication to be significantly more effective than placebo in treating each condition independently with effect sizes greater than those of other AUD (e.g., NAL) and PTSD (e.g., SSRIs) medications. There is also a practical reason for why it is important to study TOP further in VA. A review of the VA National Patient Care Database from 2009 to 2012 of the use of FDA approved and off label prescriptions for Veterans with AUD found that TOP was prescribed more often than known treatments for AUD including acamprosate, IM naltrexone, and disulfiram combined [6]. Given this frequent use across VA and extremely high rates of comorbidity between AUD and PTSD in the VA [7], it is particularly important to study TOP with PTSD treatment in the Veteran population.

A recent pilot study [10] evaluating TOP's ability to reduce drinking in Veterans receiving heterogeneous treatments for PTSD found that it decreased alcohol consumption, cravings, and PTSD symptom severity, especially hyperarousal symptoms. Importantly, TOP was well tolerated, cognitive side effects were transient, and there were no group differences in dropout and no dropouts due to adverse events. As noted by Petrakis and colleagues [42], the lack of group differences in dropout may be due to the flexible dosage schedule and because the benefits of the treatment may have offset any adverse effects. Therefore, in the proposed study, we will use a similar flexible dosage schedule with similar slow upward titration.

PE and TOP Show Promise to Act Together to Improve AUD/PTSD Outcomes. While studies have found that individuals with AUD/PTSD can benefit from PE, and that PE is more effective for reducing alcohol use and PTSD symptoms for individuals with AUD/PTSD than other treatments, drop out is high and effects are modest relative to PE with individuals who do not have AUD [8]. Individuals with comorbid AUD/PTSD often drink alcohol maladaptively to cope with stress, PTSD symptoms, and problems associated with PTSD. In addition, some individuals who take part in PE may experience increases in cravings and PTSD symptoms early in PE treatment, which may lead to poor treatment engagement or dropout. [9] Core PTSD symptoms such as avoidance and hyperarousal can interfere with ability to engage in or benefit from treatment. TOP is believed to decrease alcohol reinforcement and the propensity to drink by reducing craving for alcohol through antagonism of glutamate receptors and inhibition of dopamine release. In addition, TOP (which, as noted, is unique among AUD medications in that it helps to reduce PTSD symptoms) may reduce PTSD symptoms that may otherwise interfere with treatment engagement and may off-set PE-related PTSD symptom exacerbation which might otherwise lead to treatment dropout [10]. There is also evidence that TOP attenuates stress-induced alcohol consumption [11], perhaps by modulating glutamatergic neuroplasticity [43], which further supports the hypothesis that TOP may help reduce drinking in individuals with PTSD who have exacerbation of stress or stress related symptoms during PE. Early reductions in PTSD symptoms and cravings during PE increase the likelihood that individuals with AUD/PTSD benefit from PE and successfully reduce their drinking [12]. Thus, by helping Veterans reduce cravings and symptoms that may cause dropout or poor engagement early in treatment, TOP may increase the likelihood that habituation and

cognitive emotional processing are successful in PE, allowing psychological and functional recovery to occur.

We will evaluate parts of this proposed model regarding how TOP and PE will work together to improve AUD/PTSD outcomes through our exploratory aims (see Section 2). Thus, this proposed study will take the critical next step of evaluating whether adding TOP to PE to treat Veterans with AUD and PTSD improves psychological and functional recovery and will examine the mechanisms through which this combination of treatments may drive recovery.

Addition of saliva sample for genetic testing

Dr. Victoria Risbrough will help to conduct genetic testing on our subject population to examine role of the candidate genes in predicting treatment response. We will test the hypothesis that candidate genes related to topiramate pharmacokinetics and dynamics are associated with treatment response to topiramate. We will also examine if the topiramate effects are moderated by genes known to moderate treatment response, such as COMTval158met.

Repository: We will bank these samples with the CESAMH Biorepository (H150080) to be merged with other VA and NIH studies of PTSD genetic risk for future sequencing, methylation and Genome Wide Association Studies.

Section 9 - Design and Methods

9) Describe the research design and the procedures to be used to accomplish the specific aims of the project. Provide a precise description of the planned data collection, analysis and interpretation. Address sample size, inclusion of women and minorities. Define in clear terms exactly what will be done to the human subjects.

Design. This prospective, randomized, controlled trial will assess the efficacy of PE+TOP as compared to PE+PLA. Medical providers, participants, and evaluators will be blinded to the intervention condition. TOP or placebo will be administered over 16 weeks (6 weeks of upward titration and 10 weeks at maximum target dose up to 250mg per day) of active treatment, and participants will be asked to complete 12 sessions of PE during those 16 weeks (allowing for missed appointments, which are common among individuals with AUD and PTSD). Ongoing assessments of primary outcomes (i.e., heavy drinking days, PTSD symptoms, functional impairment) will be made at baseline, post-treatment, and 3- and 6-months following treatment completion. Our hypotheses are that the combined intervention (PE+TOP) will be more effective in reducing heavy drinking events and PTSD symptoms and in improving functioning and quality of life than PE with placebo (PE+PLA) among male and female Veterans with AUD and PTSD diagnoses. One hundred twenty (120) participants will be recruited through San Diego VA addictions and mental health treatment programs and randomized at the individual level. All symptomatic and interested participants who do not receive TOP during the trial will be offered the treatment immediately after blind is broken following the final assessment. In order to ensure we are examining outcomes in a multifaceted and informative manner, we will include assessments of primary comorbid conditions and multiple domains of functioning to provide the most comprehensive and informative data to inform clinical practice with this complicated population. Biweekly self-report assessment of substance use, cravings, and PTSD and depression symptoms will be completed. We will also examine differential drop out, early response, and treatment adherence.

Participants will have up to 16 weeks (while they take TOP or PLA) to complete the 12 sessions. Consistent with our other studies of PE with AUD/PTSD samples, during the first five minutes of session, therapists will query participants about cravings and alcohol use since the last session and check in with participants regarding progress toward their alcohol use goals. This 1) allows therapists to assess whether there is increasing alcohol or other substance use that may necessitate referring the Veteran to a higher level of care (see Human Subjects), 2) gives therapists important clinical information about whether participants are using alcohol in a way that may interfere with PE mechanisms (e.g., drinking just before or after exposure assignments), and 3) gives therapists the ability to support participants in achieving their alcohol use goals in a fashion consistent with the approach used by study physicians at the medication appointments [63].

Participants will be informed of the risks associated with the use of Topiramate, including all clinically significant warnings provided by the manufacturer in the medication package insert. This includes all current warnings and cautions in the most recent FDA guidelines dates May 2019[95]. Given our frequent monitoring and standardized assessment of mood changes, we are already in compliance with the FDA's recommendation to monitor for this potentially rare adverse event. Participants will be informed that, as with any drug, Topiramate administration may involve other risks that are not known at the present time. If the study staff learns of any new possible risk or side effects of this drug, participants will be notified immediately. Participants will be informed that their condition may remain the same or deteriorate due to an ineffective treatment. They will also be informed of the availability of alternative treatments to facilitate alcohol use reduction. Participants will be told that if, in the opinion of the doctor, there are problems caused by their participation in the study that make it unwise for the participant to continue, their participation will be stopped. Patients who are discontinued from the study for any reason will be given a referral for further treatment if indicated.

TOP Titration Schedule, Dosage Considerations, and Duration of Treatment. To increase medication tolerability, dosages of TOP will be gradually titrated upward (weeks 1-5) on a fixed schedule as shown in Table 1 . Participants will continue on this dosage of medication for 10 weeks (weeks 6-16) until a more rapid dosage titration (i.e., 50 mg twice daily for 4 days, then 25 mg twice daily for 3 days) downward occurs. This latter dosage titration is intended to minimize any discontinuation syndrome that may occur in patients treated with TOP.

Several prior studies of TOP have used a maximum target dose of 300 mg [5]. However, a recent meta-analysis of TOP found 200 mg to be effective for treating AUD [5] and VA/DoD guidelines recommend 200 mg per day for the treatment of AUD due to lower side effects than at 300 mg [2]. We made the decision to use TOP at a maximum target dosage of up to 250 mg to take into account the recent findings and recommendations as well as the literature that used 300 mg as the maximum dosage. Therefore, we will use a maximal target dosage of 250 mg. in these AUD/PTSD participants and will carefully monitor adverse effects .

Every attempt will be made to maintain participants at the maximal TOP dosage specified above. Studies by us and other investigators using maximal dosages of TOP of approximately 200 mg per day have found that approximately 90% of participants were able to take the full maximal dosage. However, participants who are unable to tolerate the specified dose will be allowed to continue in the study at a reduced dose (the maximum tolerated dose) as determined by the research physician. Such participants may continue to participate in all other aspects of the study. When TOP/placebo dosage reduction is warranted due to adverse side effects, the research physician will decrease the medication dosage by one step at a time as shown in the dosage titration schedule from the maximum to the amount that is clinically tolerable. As dosage reductions are permissible in all groups, this will not break the blind. In the case of severe side effects, discontinuation of the study agent may be necessary. In such a situation, a research physician will evaluate the patient to determine whether the study agent should be discontinued immediately or should be tapered to discontinuation.

Participants will have medication appointments weekly for the first six weeks and every other week until week 16. Medication appointments will be 30 minutes in length. In order to maintain high compliance with the TOP regimen, all participants will receive Medical Management Counseling [MMC; 60] at their TOP appointments. MMC is a manualized supportive counseling method designed by the National Institute of Alcohol Abuse and Alcoholism to promote adherence to the medication regimen and reduction in alcohol use. Study physicians will complete a three hour training and participate in monthly calls led by Drs. Stein, Brody, and Matthews to ensure standardization of pill administration and the MMC protocol.

The 16-week double-blind treatment phase is designed to incorporate the dosage titration period and to allow a 10-week period where active medication is at steady-state concentrations. Thus, both the medication period and the psychotherapy period will be 16 weeks, during which participants are anticipated to attend up to 12 medication and psychotherapy appointments. This schedule also makes it such that patients will reach their maximum therapeutic dose of TOP at the time that they begin imaginal exposure in PE.

Imaginal exposure is considered a high risk time for dropout or disengagement [14]. In our model, we propose that TOP's GABA-facilitatory and glutamate inhibitory mechanisms will help participants engage in and benefit in PE by reducing cravings and PTSD symptoms early in treatment (see exploratory aims).

Our plan for slow titration and flexible dosage is consistent with other studies that have found TOP to be well tolerated, cognitive side effects to be transient, and no group differences in dropout between TOP and placebo due to adverse events [10].

Phone, mail, and Telehealth Appointments: Generally, all appointments typically conducted in-person (therapy, medication, consenting, assessments, etc.) can be conducted via phone, mail and/or VA approved secure Telehealth communication software as needed. This will help to ensure continuity of all study precedures while reducing other risks related to in-person contact.

Medication Blinding Plan. Study participants and treatment providers will be aware that participants will receive either active or inactive medications and that all are kept blind to medication received until the conclusion of the study. Dr. Steven Funk, the non-blinded VA San Diego Research Pharmacist, will assign participants to treatment group based on our randomization procedures and will manage the double blind. TOP and placebo tablets will be obscured by mixing with lactose, and over-encapsulated in identical opaque locking capsules to ensure blinding. The Research Pharmacist and a non-blinded, non-treating physician Safety Monitor (Tonya Masino, M.D.) will have access to the medication randomization record in the event that the blind must be broken on an emergent basis.

Medication Dispensing. Study medication will be stored in the VA San Diego Research Pharmacy. Storage, packaging, dispensing and record keeping will be the responsibility of the Research Pharmacist, Dr. Funk, in coordination with the study staff (i.e, the study coordinator and therapists) and Study Physicians. During the two dosage titration periods, capsules will be packaged in vials in accordance with the graduated dosing schedule described in the Titration section above. During the 10-week maintenance phase, capsules will also be packaged in vials by the pharmacist to be dispensed to participants at each scheduled visit. In the event that a participant misses a morning dose in the twice-daily dosage schedule, they will be instructed to take it later in the day. In the event that the patient entirely misses a daily dose, they will be told not to double-up on the capsules the following day. Since medication adherence is the focus of one of the concomitant psychosocial interventions, missed doses, problems with adherence, and strategies to improve compliance will be discussed regularly with each study participant. Participants will be asked to return unused medication at each visit to the Research Associate for capsule counts. Unused medication will be destroyed as per VA San Diego Research Pharmacy protocol.

All participants will receive PE psychotherapy for PTSD. Although several treatments have been found effective in treating PTSD, we have selected PE based on its particularly strong empirical record and its appropriateness given study aims. The evidence for PE efficacy is greater than that for any other PTSD intervention, and treatment effects are generally maintained during follow-up. Thus, the safety and tolerability of PE is well documented for patients with and without AUD, and, because of Dr. Norman and other investigators' experience administering and disseminating PE for patients with and without AUD, the study team is exceptionally well prepared to utilize this intervention.

PE [19] includes breathing retraining; psychoeducation; prolonged, repeated exposure to trauma memories (imaginal exposure); processing of trauma related material that emerges during exposure; and repeated real life exposure (in-vivo) to trauma-related avoided situations. Participants will practice in vivo exposure and listen to audio of imaginal exposures between sessions. PE is delivered over 12 weekly sessions. Ideally, participants attend therapy each week; however, participants sometimes miss appointments. Therefore, participants will have up to 16 weeks (while they take TOP or PLA) to complete the 12 sessions. Consistent with our other studies of PE with AUD/PTSD samples, during the first five minutes of session, therapists will query participants about cravings and alcohol use since the last session and check in with participants regarding progress toward their alcohol use goals. This 1) allows therapists to assess whether there is increasing alcohol or other substance use that may necessitate referring the Veteran to a higher level of care (see Human Subjects), 2) gives therapists important clinical information about whether participants are using alcohol in a way that may interfere with PE mechanisms (e.g., drinking

just before or after exposure assignments), and 3) gives therapists the ability to support participants in achieving their alcohol use goals in a fashion consistent with the approach used by study physicians at the medication appointments [63].

Recruitment. Eligible participants will contact our study in response to 1) flyers posted in VA mental health, primary care, and alcohol and substance use treatment programs; 2) advertisements in print and web-based media; 3) referrals from VA primary care, SAMI, PTSD, and other psychiatry clinics and 4) from other research studies who's participants provided consent to contact. Following verbal consent, potential participants will undergo an initial screening that takes approximately 30-45 minutes to complete. The screening, used in the PI's current CSR&D merit study, is intended to detect clinically significant alcohol use and PTSD symptoms. It consists of screening items from the SCID [52] and the Posttraumatic Stress Disorder Checklist-5 [PCL-5; 53] for disorders that are part of the inclusion and exclusion criteria. Those who meet study criteria will attend an in-person interview where they will sign informed consent documents and take part in a baseline assessment (see measures in 9.8.). Following baseline assessment, participants will have the opportunity to meet with a research study therapist to talk about their goals for taking part in the study treatments and the pros and cons of taking part in the study. Following the session, participants who choose to proceed with study participation will be randomized to the intervention or control condition. Random permuted blocks will be used which ensure exactly equal treatment numbers at certain equally spaced points in the sequence of patient assignment. A computer-generated randomization sequence will be provided by our and held by Dr. Steve Funk study pharmacist. *Randomization will be stratified by whether or not the participant is on a anti-relapse medication. It is expected that randomization will balance out severity of PTSD symptoms, severity of alcohol use, and functional impairment, and this will be assessed in analyses excluded.*

Women and Minorities
Women comprise 11% (e.g., SAMI clinic) to 60% (Military Sexual Trauma clinic) of the Veterans seen in the clinics from which we will be recruiting, and approximately 24% of Veterans in the program are minorities. Consistent with SAMI demographics as a whole, 10% of participants in our current Merit study over the past 3 years have been women. We have been able to obtain 26% Hispanic, 16% African American, and 20% other ethnic groups, for a total of 52% from minority groups. We will continue attempts to oversample these groups to obtain adequate recruitment of females and minorities to examine effect sizes for these groups relative to male and Caucasian counterparts.

Verification of Pregnancy Women that are pregnant , lactating, or plan to become pregnant during the period of participation in the study will be excluded from participation. All eligible participants will receive a laboratory diagnostic evaluation consisting of a chemistry panel, complete blood count, liver function tests (LFTs), urine toxicology screen and pregnancy test during their screening and/or randomization appointments so that participants with any illnesses that might adversely be affected by their participation in the trial will be excluded. Veterans will be sent to VA laboratory to have blood work completed. No research staff shall have contact with blood/specimens.

Treatment Setting. All work will be carried out at the Substance Abuse Mental Illness (SAMI) outpatient program of the Alcohol and Drug Treatment Program (ADTP) of the VASDHS. The SAMI program was established in 1991, with > 4500 outpatient visits per year. Referrals to SAMI come from ADTP (15,000 outpatient visits per year, and a 28 bed, 28 day residential program with > 360 residents annually), inpatient Psychiatric Unit (> 800 admissions/year), outpatient Mental Health Program (> 16,500 visits/year), and Primary Care (>12,000 Veterans/year). Services in the SAMI clinic have grown in recent years with a 33% increase in the number of Veterans receiving care. The staff includes a clinical psychologist, social worker, and trainees (psychology interns and postdoctoral fellows, and social work interns); psychiatry providers are coordinated through the larger ADTP and Mental Health service.

Standard Pharmacotherapy. Pharmacological treatment will be provided at no cost to the proposed project. The VA follows treatment guidelines that require standardized prescribing practices for individuals with PTSD, depression, and AUD. We expect at least 85% of

participants will be receiving medications based on these guidelines. We recognize that pharmacotherapy and changes in medications will be an uncontrolled source of variance but expect that any changes will be similar across treatment conditions and thus balanced by randomization. We considered recruiting participants who were not on medication or asking participants to be medication stable prior to study entry. However, psychotropic medications have well documented effectiveness for the treatment of PTSD and withholding such medication would be inappropriate for this high-risk population. The only exception is if participants are on addiction mediations they will be asked to stay on a stable approved dose at least two weeks before starting the study drug and throughout the study. Study coordinators will record from VA medical records and patient self-report all treatment (psychotherapy and medication) in which Veterans participate in the VA. Participants will also be asked about treatment outside of the VA. We will compare treatment as usual between our two conditions and, if differences in any variables are found, include these as covariates in analyses.

Blind. All investigators, clinicians, and study staff will be blind to treatment condition. Only the research pharmacist will know to which group participants have been randomized. The success of the blinding procedure will be evaluated by having the rater guess the patient's assigned treatment condition after each assessment. If indicated, participants will be asked to go through detoxification prior to beginning the study. Detoxification programs are available on inpatient and outpatient bases through programs funded by the San Diego VA.

Sources of Materials: The data relevant to the proposed project will be gathered strictly for research purposes. Blood and urine specimens obtained are for clinical and research purposes only. Sources of research data will be demographic data collected from participants recruited for this study, ratings from independent clinical evaluators, patient self-reports, toxicology screens, and through VA CPRS chart review.

Treatment Integrity Evaluation of PE. Treatment integrity consists of two components of therapist administration: (1) therapist adherence and (2) therapist competency [61]. Therapist adherence refers to the extent to which the therapist used the interventions prescribed in the intervention protocol. Therapist competency refers to the level of skill shown by the therapist in delivering the treatment. Therapist adherence and competency will be monitored by two methods: clinical supervision with Drs. Norman, Haller and Davis, and independent evaluation by Dr. Haller. Our approach to treatment fidelity and adherence utilizes accepted standards [62] including: (1) treatment manuals with weekly objectives, outcomes, and agendas, (2) therapist training, and (3) ongoing evaluation of treatment fidelity through audio-rating of therapy sessions and supervision. To identify problems early, one of the supervisors will listen to at least 3 audio-recordings of each therapist and complete fidelity rating sheets for each session. Corrective feedback will be provided as needed. Thereafter, the supervisors will rate occasional audio-recorded sessions . Further, the supervisors will have weekly supervision of therapists to evaluate their implementation of and adherence to the therapy manual. The participant evaluation method of quality assurance involves asking each participant to complete a brief checklist that queries the content of the session (e.g., "Did the therapist discuss common reactions to trauma?"). In addition, therapists will keep a session-by-session "PE Session Tracking Form" which includes self ratings about the "% of time" of each session was spent "using the manual" and covering the relevant module content.

Quality Control - Data entry and management. Data will be collected on paper forms and checked for missing items. Participants will be queried at time of collection to complete or clarify blank or illegible responses. Refusal or inability to respond to items will be documented with explanations. Data will be entered into SPSS databases using a system that incorporates checking for out of range values and requires all data to be entered twice, with discrepancies corrected at time of entry. Data will be stored in locked file cabinets.

Statistical Considerations:

- **Data Management**. In the initial 3 months, data management procedures will be developed and implemented. Data entry and quality assurance will be ongoing during enrollment, with validation and double-entry procedures in place to ensure accurate data entry. Study staff will be trained to limit missing data by checking questionnaires

immediately and prompting for additional response and re-contacting participants if necessary. Study staff will attempt to collect all post-randomization data regardless of treatment attrition.

- **Statistical Analysis**. Data analysis will occur in a staged approach, moving from initial descriptive analyses to hypothesis tests. Descriptive statistics and plots will summarize and assess distributional properties of key variables. Randomized groups will be compared on baseline demographic and clinical variables using analysis of variance, 2, or Wilcoxon-rank sum tests. Any baseline variables potentially confounded with treatment condition will be incorporated in the primary analyses as covariates. Outliers will be assessed and variables whose distributions depart significantly from normality will be transformed.
- **Missing Data**. The primary outcome will be tested using an intent-to-treat framework. If, the extent of missing data is small and the data appear to be consistent with a missing-at-random model (MAR) [84], then the maximum likelihood analysis using all randomized cases and the observed data is an appropriate method for handling the missing data [85]. In the MAR model the missingness can be a function of the observed covariates and observed outcomes. If the missingness is related to the unobserved outcome, then the missing values are considered missing not at random (MNAR). However, the MAR assumption has been shown to be plausible even in studies such as substance abuse in adolescents [86]. The critical element when conducting MAR-based analyses is to include covariates related to the missingness in the statistical model [87]. As a check on the sensitivity of our conclusions to the assumption that the missing data are MAR we will conduct pattern-mixture modeling, which is appropriate with data is likely MNAR [88, 89]. In these models participants are categorized into groups based on patterns of missing data over time. Missing data pattern groups are then included as covariates in the statistical model and the effect of missing data on parameter estimates can be determined. Parameter estimates can be averaged over the missing patterns to adjust for biased estimates.
- **Power analysis:** We determined sample size for a two group design with PHDD as the primary outcome at post-treatment. A recent meta-analysis comparing the effects of TOP compared to placebo on heavy drinking found an overall standardized effect size of .406 [5]. The overall effect size was determined from seven studies with effect sizes ranging from .140 to .623. To ensure adequate power we calculated a sample size for a two-sample t-test by condition. The proposed primary analysis uses PHDD measured at baseline, post-intervention, 3, and 6 months in a random-intercepts regression model; however this use of additional data should serve to increase the power. A two-tailed test would require a sample size of 192 participants to detect an effect size of .406 with 80%. This is not a feasible sample size to recruit within the study's recruitment window. Alternatively, a 1-tailed test requires a sample size of 120 to have 72% power to detect the expected effect size. A one directional test is warranted given we are interested only in the improvement of PHDD for the TOP condition compared to the placebo condition. In addition, a sample size of N = 120 provides 80% power for a two-tailed test to detect a sample size of .516, a somewhat larger effect size within the range of effect sizes pooled in the recent meta-analysis [5]. Overall, we believe a sample size of N = 120 balances three needs: (1) sufficient power to compare the study groups; (2) the reality of recruiting a sample of Veterans with AUD and PTSD; and (3) overall project cost considerations.

Aims:

- **Primary Aim Analysis**. As stated in Aim 1, we will evaluate the efficacy of PE+TOP, as compared to PE+PLA, in percent heavy drinking days (PHDD) among Veterans with comorbid AUD/PTSD at post-treatment and 3- and 6-month follow-up. The statistical model will be a generalized linear mixed model with a log link and gamma distribution variance function. If the over-dispersion parameter is close to zero a Poisson regression model will also provide equivalent model fit. The model will include a factor for treatment condition (PE+TOP, PE+PLA) and a linear term for time (baseline, post-treatment, 3, and 6 month follow-up). This model can be expanded to determine an adjusted intervention effect by including covariates such as gender and era of service. The primary test of treatment effect will be a group x time interaction. This flexible analytic method provides maximum likelihood parameter estimates based on all of the available data, allowing for the inclusion of cases with missing data and the modeling of the covariance error structure of the data across the

assessment points [90]. If the extent of missing data is small and the data appear to be consistent with a missing-at-random model, we will also carry out maximum-likelihood based on a "completer-analysis" using the observed data.

- **Secondary Aim Analyses**. As stated in Aims 2 and 3, veterans in PE+TOP, compared to PE+PLA, will show greater improvements in PTSD, depression symptoms, functional impairment and quality of life at post-treatment and 3- and 6-month follow-up. We will first examine the relationships among these outcomes to determine if composite scores should be created from highly correlated variables. This will help to reduce the number of statistical tests. The statistical model for these analyses will be random effects regression models as described in the primary aim analysis section, using identity link for Gaussian distributed linear variables and log or logit link functions for discrete or skewed outcome variables. These analyses would be in an intent-to-treat framework using maximum likelihood as before.
- **Exploratory Aims**: First, we will explore the extent to which lower drinking and PTSD symptoms are associated with better functional outcomes. Analyses will build on the secondary analysis models, where functional impairment (WHODAS, WSAS) serve as the dependent outcome variables in GLMMs. The exploratory analysis measures of percent heavy drinking days (PHDD) and PTSD symptom severity (CAPS) will be added as time-varying covariates in separate GLMMs, to examine whether lower drinking and lower PTSD severity are associated with better functioning. We will also explore prospective or "lagged" effects for these time-varying covariates (PHDD /CAPS), to test temporal precedence as an indication of drinking/PTSD severity as potential mechanisms of improved functioning. Second, we will test the mediating effect of alcohol cravings and PTSD symptoms on the direct effect of the interventions on heavy drinking. Using the recommended analytic framework for multilevel mediation in interventions [91], separate HLMs will examine the "a" path (intervention effect on mediator) and "b" path (mediator effect on outcome). The mediated effect will be estimated using the product-of-coefficients approach and statistical significance estimated with 95% CI's via the bias-corrected bootstrap [92]. Third, we will test the mediating effect of change in cognitive functioning from baseline to mid-treatment on the strength of the direct effect of the intervention on PTSD symptoms and SUDs. The same analytic framework for testing statistical mediation will be used as described above.

Genetic Testing

- For each gene candidate we will conduct a 2 way repeated measures ANOVA on the data from the participants in the topiramate arm (approximately 74 participants), with genotype as a between subject factor and time (baseline, 2 mo, 5 mo and 8 mo) as a within subject factor. We predict that genotype will moderate change in CAPS scores over time as supported by a genotype X time interaction. The same analysis strategy will be used on the non-topiramate arm to determine if genotype affects overall treatment response, or only response specific to topiramate

- Covariates: ancestry, sex, medication status, and baseline CAPS scores. We will correct for multiple comparisons based on number of gene candidates tested as appropriate.

DNA Sampling

- Subjects will be asked for a saliva sample for immediate storage using an Oragene salivary sample kit. Using this kit allows for DNA quality that is similar to that of blood (99% concordance for SNP and CNV assessments between salivary and blood samples using this storage method), unlike mouthwash or buccal swab samples. Mouthwash samples are also not ideal due to having alcohol content which is inappropriate for this participant group. We felt that an invasive blood draw was also unnecessary given the high quality DNA sampling allowed for by the Oragene Discover kit. We will determine genetic ancestry using a small panel of 41 multiplex ancestry informative markers. The genotypes from the ancestry markers will be used to determine continental ancestry to construct principal components to be included as covariates.

DNA extraction and genotyping

- We will utilize the VMRF CFAR genomics core and standard extraction from Oragene salivary samples and polymerase chain methods as previously described by (Kolassa et al. 2010; Valente et al. 2011a) for COMTval158met genotyping. Genotype frequencies will be tested

against Hardy Weinberger Equilibrium using Pearson's goodness of fit 2.

Power Analysis:

Using Gpower we calculated that a total N of 75 will give us 0.9 power to detect a small-moderate effect size (f=0.4) of genotype if the SNP is common (e.g. 25/50/25 ratio in general population) using a 2 way repeated measures ANOVA (gene with 2 levels and time with 4 levels). For a t-test comparing final outcome measures post treatment, we have 0.8 power to detect a d=0.75 effect size with this N

- Repository: We will also use these samples for future sequencing, methylation and Genome Wide Association Analysis and merge genotype data and diagnostic data with other VA and/or NIH studies to increase power to discover new genetic associations with PTSD and PTSD treatment response

fMRI

Participants will be asked if they are interested to take part in the optional fMRI study titled "Neuromarkers of Treatment for Comorbid Posttraumatic Stress Disorder and Alcohol Use Disorder IRB # H170116 (P.I. Andrea Spadoni-Townsend, PhD). If participants consents to be contacted for the optional study, Dr Spadoni-Townsend's approved research team will contact patient and if patient agrees they will consent them for the study. Dr. Sonya Norman and her research team may share some of thier data with Dr. Spadoni-Townsend's approved research staff for the purpose of data analysis if the participant initals the appropriate box in the consent form to allow data sharing.

COVID-19 Procedures

Temporary procedures to allow for participation while maintaining social distancing:

The protocol remains as approved with the following exceptions. If a Veteran is potentially interested in participation after the initial contact and screens eligible using the telephone screening, an enrollment appointment will be scheduled using VA approved secure Telehealth communication software or telephone. We will send an encrypted email (using VA Azure RMS), a message through MyHealtheVet and/or send documents by US mail containing (1) the approved ICF, (2) the approved HIPAA document, (3) the CA Experimental Subjects Bill of Rights, and (4) fillable PDF baseline assessment documents, and arrange a telehealth or through VA approved secure Telehealth communication software to complete the informed consent process, explain the HIPAA Authorization, and CA Experimental Subjects Bill of Rights. If the visit is completed by VA approved secure Telehealth communication software, the staff member will witness the signing of the ICF and HIPAA Authorization and will instruct the potential participant to provide documentation of written informed consent by one of the following methors: (1) returning images of the documents through MyHealtheVe (2) by allowing a screenshot of the signed documents (approval date and signature must be clearly visible) (3) study staff can have the participant digitally sign the fillable PDF documents which can be saved directly to the R Drive (4) or document can be signed and returned via encrypted email (using VA Azure RMS) (5) documents can be sent and signed via DocuSign. If documents were mailed, the patient will be instructed to mail back the signed documents. These electronic documents will be stored electronically separate from study data on the R: drive. Paper documents will be stored securely according to VA requirements.

If the visit is done by phone, the (1) the approved ICF, (2) the approved HIPAA document, (3) the CA Experimental Subjects Bill of Rights, and (4) baseline assessment documents will be emailed (using VA Azure RMS and the participant will need to print all documents) and/or hard copied will be mailed to the participant. Study staff will call the participant at the scheduled appointment time to complete the documents. Study staff along with the participant will complete the informed consent document, explain the HIPAA Authorization, and CA Experimental Subjects Bill of Rights. The participant will be instructed to mail back the signed consent and HIPAA forms. Once the forms are received by study staff, the baseline assessments will be scheduled and completed by phone or through VA approved secure Telehealth communication software.

Participants will be sent a copy of the signed and dated forms, regardless if the Informed Consent appointment was completed by VA approved secure Telehealth communication software or by phone.

Once documentation of written consent is received, the staff member will begin the baseline eligibility assessment. The participant may use the fillable PDF to complete the self-report forms and return them via MyHealtheVet, may read their responses to the items to a staff member who will transcribe the responses into an electronic form behind the VA firewall or docum

ent can be signed and returned via encrypted email (using VA Azure RMS). The interview-based measures will be completed and electronically transcribed. Safety concerns will be reviewed with a licensed mental health provider (e.g., suicidality). Refer to the *Risk Management* section of the protocol for telephone safety procedures.

Eligible participants will be required to complete laboratory diagnostic testing at the VA location of their choice. This is the only visit that the veteran is required to attend in person. Following laboratory diagnostic testing, the veteran will be scheduled for all remaining baseline medical and psychology meetings by telephone and/or VA approved secure Telehealth communication software.

Following the baseline eligibility appointments, if the veteran is found to be eligible for the treatment potion of the study, they will be randomly assigned to PE + Placebo or PE + Topiramate. All psychiatry and therapy appointments will be scheduled through VA approved secure Telehealth communication software or phone. We will send an encrypted email (using VA Azure RMS), a message to MyHealthyVet, or send documents by US mail containing all therapy and psychiatry materials to be used throughout the treatment portion of the trial. The participant may use the fillable pdf's to complete the forms and return them via MyHealtheVet, may read responses to the items to a staff member who will transcribe the responses into an electronic form behind the VA firewall, or they may be returned via encrypted email (using VA Azure RMS).

Assessments will be administered again at mid-treatment, immediately after completion of the treatment potion of the study, at 3-month post-treatment, and finally at 6-month post-treatment, using phone and/or VA approved secure Telehealth communication software. We will send an encrypted email (using VA Azure RMS), a message to MyHealthyVet, and/or send documents by US mail containing assessment materials to the veteran. The veteran will submit the completed assessment materials by either returning images of the documents through MyHealtheVet, mailing back completes self-report assessments, or a staff member may read questions and responses will be transcribe into an electronic form behind the VA firewall, or they may be returned via encrypted email (using VA Azure RMS). The interview-based measures will also be completed and electronically transcribed.

Participant compensation - Vendorizing is now accepting digital signatures on all 10091 forms. Users who are registered in CEP (Customer Engagement Portal) will be able to submit vendor forms electronically. The participant may also use the fillable pdf to complete the form and return them via MyHealtheVet, they may be mailed a blank 10091 form to be mailed back to study staff for submission and payment, or they may be returned via encrypted email (using VA Azure RMS)..

Section 9.1 Clinical Procedures

9.1) Differentiate research procedures (or any procedures done for research purposes only) from clinical procedures (procedures that are done as part of standard care).

(Note: this differentiation should be clear in the consent form as well)

The experimental portion of this study is to test if existing psychotherapy (PE) + TOP or PE +Placebo (PL) will be effective in helping individuals who are having difficulties with alcohol use cope with the negative consequences of having experienced a traumatic event. Clinical procedures employed in this study are: the use of Exposure therapy (PE) and Topiramate(Top).

Section 9.3 Non-IND Drugs

9.3) List all other (non-IND) drug names and dosages given for research purposes. Document why an IND is not required (see ? for detail)

Non-IND Drugs:
The following are the FDA criteria for Exempt from IND requirements:
A clinical investigation of a marketed drug is exempt from the IND requirements if all of the criteria for an exemption in § 312.2(b) are met:
• The drug product is lawfully marketed in the United States. - YES
• The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug. - YES
• In the case of a prescription drug, the investigation is not intended to support a significant

change in the advertising for the drug. - YES
• The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)). - YES
The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50). - YES
• The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product). - YES

Topimarate (TOP). TOP is approved by the FDA for three indications: treatment of epilepsy; prophylaxis of migraine headaches; and, in combination with phentermine, for obesity. It is also used clinically either to reduce drinking in problem drinkers, or as an aid to prevent alcoholism relapse in alcohol dependent participants. After reviewing the literature, we have chosen TOP as the optimal medication for the present trial for several reasons: 1) This medication has an extensive record of safety (several million patient-years) in a variety of diverse patient populations [55] that includes children, individuals with AUD, and patients with PTSD; and animal studies suggest that the abuse liability of TOP is low. Furthermore, TOP did not potentiate the cognitive and motor effects of alcohol in a clinical trial [56]. 2) It is the one medication that appears in meta-analytic reviews as an effective agent for both alcohol use disorder [5, 41] and PTSD [3, 57], and a recent pilot study [10] found that it decreased alcohol consumption, craving, and PTSD symptom severity in Veterans with AUD and PTSD. 3) TOP's GABA-facilitatory and glutamate inhibitory (via AMPA/kainate receptor blockade) effects make it a promising pharmacotherapy in AUD/PTSD patients, and there is preclinical evidence that the drug mitigates stress-induced drinking [11]. These mechanisms differentiate it from other AUD medications such as naltrexone and make it uniquely promising for the treatment of comorbid AUD/PTSD together with evidence based PTSD psychotherapy. 4) Its metabolites are relatively inactive and its major elimination route is renal [58]. 5) The oral preparation is rapidly absorbed and has excellent (> 80%) bioavailability. 6) Its pharmacokinetic properties are also advantageous over some of the other agents in this class because they allow for twice daily dosing without the build-up of long-acting metabolites, and the medication is regarded as safe with respect to pharmacokinetic drug interactions [59]. Initial side effects appear to subside; and slow titration, as we propose in our study (see 6.E.1.a.), is associated with low side effects [10] and high tolerability.

• TOP Titration Schedule, Dosage Considerations, and Duration of Treatment. To increase medication tolerability, dosages of TOP will be gradually titrated upward (weeks 1-5) on a fixed schedule as shown in Table 1 below.
Participants will continue on this dosage of medication for 10 weeks (weeks 6-16). until a more rapid dosage titration (i.e., 50 mg twice daily for 4 days, then 25 mg twice daily for 3 days) downward occurs. This latter dosage titration is intended to minimize any discontinuation syndrome that may occur in patients treated with TOP.
Several prior studies of TOP have used a maximum target dose of 300 mg [5]. However, a recent meta-analysis of TOP found 200 mg to be effective for treating AUD [5] and VA/DoD guidelines recommend 200 mg per day for the treatment of AUD due to lower side effects than at 300 mg [2]. We made the decision to use TOP at a maximum target dosage of up to 250 mg to take into account the recent findings and recommendations as well as the literature that used 300 mg as the maximum dosage. Therefore, we will use a maximal target dosage of 250 mg in these AUD/PTSD participants and will carefully monitor adverse effects. Every attempt will be made to maintain participants at the maximal TOP dosage specified above. Studies by us and other investigators using maximal dosages of TOP of approximately 200 mg per day have found that approximately 90% of participants were able to take the full maximal dosage. However, participants who are unable to tolerate the specified dose will be allowed to continue in the study at a reduced dose (the maximum tolerated dose) as determined by the research physician. Such participants may continue to participate in all other aspects of the study. When TOP/placebo dosage reduction is warranted due to adverse side effects, the research physician will decrease the medication dosage by one step at a time as shown in the dosage titration schedule from the maximum to the amount that is clinically tolerable. As dosage reductions are permissible in all groups, this will not break the blind. In the case of severe side effects, discontinuation of the study agent may be necessary. In such a situation, a research physician will evaluate the patient to determine whether the study agent should be discontinued immediately or should be tapered to discontinuation.
Participants will have medication appointments weekly for the first six weeks and every other week until week 16. Medication appointments will be 30 minutes in length. In order to maintain high compliance with the TOP regimen, all participants will receive Medical Management Counseling [MMC; 60] at their TOP appointments. MMC is a manualized supportive counseling method designed by the National Institute of Alcohol Abuse and Alcoholism to promote adherence to the medication regimen and reduction in alcohol use. Study physicians will complete a three hour training and participate in monthly calls led by Drs. Stein, Brody, and Matthews to ensure standardization of pill administration and the MMC protocol.
The 16-week double-blind treatment phase is designed to incorporate the dosage titration period

and to allow a 10-week period where active medication is at steady-state concentrations. Thus, both the medication period and the psychotherapy period will be 16 weeks, during which participants are anticipated to attend up to 12 medication and psychotherapy appointments. This schedule also makes it such that patients will reach their maximum therapeutic dose of TOP at the time that they begin imaginal exposure in PE. Imaginal exposure is considered a high risk time for dropout or disengagement [14]. In our model, we propose that TOP's GABA-facilitatory and glutamate inhibitory mechanisms will help participants engage in and benefit in PE by reducing cravings and PTSD symptoms early in treatment (see exploratory aims). For the reasons stated above, this study in my opinion meets all of the requirements, but this is the IRB's decision

Section 9.5 Data Banking

9.5) Identify what information will be retained, whether or not identifiers are included with the banked data, and provide future use examples. Indicate how the study will comply with VHA Handbook 1200.12.

A varied set of information will be retained under this protocol, given the multiple sources of contribution. Demographics, medical history, mental health information, physiologic data, and biological specimens will be maintained in the biorepository for future use in larger studies of the biological mechanisms of trauma-related disorders. These data will be used for the following: 1) To perform biological assays to understand differences in genetic, transcriptomic, epidemic or proteomic signaling across trauma-exposed individuals and controls, 2) To support research of Veterans who give consent to release their data as part of other independent HRPP-approved protocols, and 3) To support clinical standards of care and enhance quality of care for veterans. Identifiers may be included in the biorepository (if available), but will be separated from the research data and protected by the use of subject identifiers, the use of a Master List, double locked storage at the VA San Diego Healthcare System for all physical data, and pass-code protected, limited access files located on the R: Drive in the PI's study specific folder for all electronic data. Identifiers will be protected to the extent of the law as defined by the VA Handbooks 1200.12, 1605.01, and 1605.2. An example of a future use of this research information could be to test the role of a candidate gene in associations of PTSD with reduced hippocampal volume. A number of CESAMH investigators conduct imaging studies on their PTSD patients all of which collect structural imaging data. These data, along with salivary samples or genotype data if already established could be pooled across studies to test specific hypotheses of genetic interactions with PTSD that results in greater hippocampal volume differences compared to controls.

Section 9.6 Specimens

9.6) Identify the biological materials, procedures for obtaining material, the sources of the specimens.

All eligible participants will receive a laboratory diagnostic evaluation consisting of a chemistry panel, complete blood count, liver function tests (LFTs), urine toxicology screen and pregnancy test during their screening and/or randomization appointments so that participants with any illnesses that might adversely be affected by their participation in the trial will be excluded. Research staff will not conduct any of the laboratory tests or handle or come in contact with any blood/samples. Study clinicians will request the laboratory work and veterans will go to the VA clinical laboratory to have the above lab work done.
DNA Sampling:
Subjects will be asked for a saliva sample for immediate storage using an Oragene salivary sample kit. Using this kit allows for DNA quality that is similar to that of blood (99% concordance for SNP and CNV assessments between salivary and blood samples using this storage method), unlike mouthwash or buccal swab samples. Mouthwash samples are also not ideal due to having alcohol content which is inappropriate for this participant group. We felt that an invasive blood draw was also unnecessary given the high quality DNA sampling allowed for by the Oragene Discover kit. We will determine genetic ancestry using a small panel of 41 multiplex ancestry informative markers. The genotypes from the ancestry markers will be used to determine continental ancestry to construct principal components to be included as covariates (Nievergelt et al. 2013).

Section 9.7 Specimen Banking

9.7a) Select the specimen banking method(s):

9.7a1) Specimens will be banked at **VASDHS**

(•) Yes ( ) No

9.7a2) Specimens will be banked at **another VA** facility under the direction of the ACOS there

( ) Yes (•) No

9.7a3) Specimens banked at multi-site protocol banking facility **approved by VA ORD**

( ) Yes (•) No

9.7a4) External banking/storage **waiver from ORD is approved.**

( ) Yes (•) No

9.7a5) External banking/storage **waiver from ORD is submitted** and pending.

( ) Yes (•) No

9.7a6) External banking/storage **waiver will be submitted** to ORD.

( ) Yes (•) No

9.7b) Provide the banking detail - what tissues are banked, where, whether or not specimens are identified, status of waiver, etc.

Saliva will be labeled with a biorepository ID and visit number and stored in Dr. Risbrough's VA research laboratories including freezers located on the 6th floor of Building 1 (room 6180). Samples and DNA will be identified by a unique subject number code. Specimens will be genotyped conducted by CFAR, a VA affiliated core.

Section 9.8 Questionnaires & Surveys

9.8) Provide the name and a reference for questionnaires/surveys that are standard or identify them here and attach a copy of the questionnaire/survey.

The primary efficacy outcomes of interest are reduction in alcohol use (percent heavy drinking days), PTSD symptoms, and improvement in functional impairment and quality of life at post-treatment and follow-up. We will also examine rates of drop out, depression symptoms, and potential mediators and moderators such as treatment process variables and gender.

Alcohol and Substance Use Measures. At baseline, participants will be administered the AUD and SUD sections of the Structured Clinical Interview for DSM-5 [SCID; 52]. The Timeline Follow-back Procedure [TLFB; 63] will be employed at all assessment points to evaluate drinking and drug use during the 90 days preceding the screening visit. The Quantity-Frequency Index [64] and maximal consumption will be calculated for alcohol use. Drug use indices will be similarly derived for other drugs. The TLFB will be used at each follow-up to establish: % heavy drinking days (HDD), % days abstinent (PDA), time to relapse to heavy drinking, length of use episodes, severity of relapse, and current alcohol/drug use pattern. The Addiction Severity Index-5th edition (ASI) interview [65] which includes seven subscales (medical, employment, alcohol use, drug use, legal, family/social, and psychiatric), will be used to assess severity of alcohol problems. A self-report Substance Use Inventory [SUI; 66] will be administered at treatment sessions. It asks on which of the preceding seven days participants used alcohol or any of seven major types of drugs. Participants will complete an initial toxicology screen at baseline and random screens will be conducted during 25% of the assessment. Relapse episodes will be classified using the Modified Contextual Cue [MCC; 67] system for precursors using transcribed verbatim reports of relapse episodes, and using Shiffman and Wills' framework of temptation, stress, or other [68]. Craving will be measured weekly using the Penn Alcohol Craving Scale [PACS; 69]. The PACS is a well validated five-item, self-report measure that includes questions about the frequency, intensity, and duration of craving, the ability to resist drinking, and asks for an overall rating of craving for alcohol for the previous week. The PTSD-specific Alcohol Expectancies Questionnaire [P-AEQ; 46] measures alcohol expectancies related to PTSD symptoms. The instrument differentiates between alcohol dependent and non-alcohol dependent

individuals with PTSD, and has good psychometric properties.

PTSD and Other Disorders. The Clinician-Administered PTSD Scale for DSM-5 [CAPS; 70] is a standard semi-structured interview used to assess PTSD severity. Respondents select up to three of the most traumatic events they have experienced, and those events are used as the basis for assessing PTSD. The CAPS assesses each of the 20 items from the DSM-5 criteria B, C, D, and E and it has demonstrated high internal consistency, good interrater reliability, and excellent convergent validity. The CAPS can be administered in about 60 minutes, and it has the advantages of categorical (diagnostic) or dimensional scoring of PTSD. The PTSD Checklist – 5 [PCL-5; 71] is a brief self-report instrument to measure PTSD symptoms. It consists of 20 items, scored on a 0-point (not at all) to 3-point (extremely) scale, that correspond to the DSM-5 symptoms of PTSD. The PCL-5 will be completed at every other session. The Patient Health Questionnaire-9 [PHQ-9; 72] is a self-report scale listing common symptoms of depression. It is among the most widely used self-report depression measure in clinical populations, again facilitating comparison between this investigation and others. Stem questions from the SCID are used during screening for initial screening of study inclusion and exclusion criteria. The screening, used in the PI's current CSR&D merit study, is intended to detect clinically significant alcohol use and PTSD symptoms. It consists of screening items from the SCID [52] and the Posttraumatic Stress Disorder Checklist-5 [PCL-5; 53] for disorders that are part of the inclusion and exclusion criteria (see measures below and attached screening document).
The Columbia-Suicide Severity Rating Scale [C-SSRS; 73] is a standardized 8 point clinician-administered suicidal rating system designed to track suicidal adverse events across a treatment trial and covering the wide spectrum of suicidality.

Inventory of Psychosocial Functioning (IPF; 74). The IPF (Bovin et al., in press; Marx et al., 2009) is an 80-item self-report questionnaire of functional impairment across several domains including relationships, work, parenting, education, and general daily functioning over the past 30 days. Domain scores can range from 0 to 100 with higher values corresponding to higher functioning. Overall functioning score is calculated as the mean of all completed IPF domain scores. As participants may skip certain domains that do not apply to them (thus leading to different sample sizes for analyses predicting different domains of functioning), overall score is calculated as total sum of all completed IPF domain scores divided by the actual number of domains completed by the participant. In one study (Marx et al., 2009), the domain scores demonstrated internal consistency (subscale Cronbach's alphas between .76 and .91) and correlated highly with other established measures of functional impairment.

The Work and Social Adjustment Scale [WSAS; 77], a well validated self-report measure that queries additional domains of functioning will also be included. The WSAS queries functional impairment attributable to an identified problem in five different areas: ability to work, home management, social leisure, personal leisure, and maintaining close relationships. This five-item scale, rating each of these areas of functioning from 0 to 8, has been used to study the treatment of depression, anxiety, and PTSD. The well validated World Health Organization Quality of Life – BREF [78] will be used to assess quality of life. It consists of 26 items that measure physical and psychological health, social relationships, and environment. The Montreal Cognitive Assessment [MoCA; 79] is a brief, clinician-administered well-validated cognitive screening test. The MoCA will be used as a screening measure for study exclusion. A score of less than 26 is indicative of moderate or severe cognitive impairment. Participants who score less than 26 will be referred for additional evaluation and excluded, unless a qualified clinician provides clearance to participate. We will evaluate verbal memory and learning using the Hopkins Verbal Learning Test-Revised [80] and processing speed using the WAIS-IV digit symbol and digit search at baseline, mid-treatment, and post-treatment. Alternate forms will be used for administrations at different time points.

The Insomnia Severity Index (ISI; Morin & Barlow, 1993) is a widely used measure of insomnia with well established
reliability and validity. The ISI consists of seven items, three of which assess severity of insomnia (i.e.,
degree of difficulty falling asleep, staying asleep, and waking too early). The remaining questions tap satisfaction
with sleep pattern, effect of sleep on daytime and social functioning, and concern about current sleep difficulties.

The Military to Civilian Questionnaire (M2C-Q; Sayer et al., 2011) a 16-item self-report measure of post-deployment
community reintegration difficulty.

Trauma Related Guilt Inventory [TRGI] is a 32-item validated self-report measure assessing traumatic guilt. The TRGI has three scales – Guilt Severity, Distress, and Guilt Cognitions. We will use the TRGI as
one of our eligibility criteria (see inclusion criteria, section 9.4) and to monitor changes in guilt

and related
cognitions over time. Guilt severity will be the primary outcome of interest. It is computed by adding items regarding
guilt frequency and guilt intensity. Changes in guilt cognitions will be examined as a partial mediator of treatment
outcomes. Internal consistency is high for the TRGI (guilt severity = .90, distress = .86, guilt cognitions = .86).

Constrain environment- short assessment to inquire if patient had been in a constrained environment (jail, in patient, etc.) since their last study visit.

The Patient Reported Outcomes Information Systems (PROMIS) Pain Interference item banks assess self-reported consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. Pain Interference also incorporates items probing sleep and enjoyment in life, though the item bank only contains one sleep item. The pain interference short forms are universal rather than disease-specific. All assess pain interference over the past seven days.

Measures of Mechanism and Mediation. The Expectancy of Therapeutic and Medication Outcome [ETO; 81], This measure will be used to understand treatment credibility and participant's beliefs about how much the study treatments will help their trauma symptoms and alcohol problems. The Expectancy of Therapeutic and Medication Outcome is a 22-item self-report scale to evaluate participant's expectancies and beliefs about treatment credibility. It will be administered in Session 1. Questions are rated on a Likert-type scale (0-8).

The Additional Treatment Inventory (ATI) assesses additional psychiatric medications and psychotherapy sought during and after the completion of study treatment. The Client Satisfaction Questionnaire [CSQ; 82] is an 8-item self-report scale measuring satisfaction with treatment that will be used to measure participants' satisfaction with the interventions. Participants will also complete content specific questionnaires for each intervention at the end of each session. Process measures will include number of sessions attended, homework compliance, and tardiness.

Medication Adherence and side effects. We will use interview and pill counts as the primary assessments to measure adherence. To expand upon the reliability of this information, medication will be dispensed weekly in vials showing morning and evening doses separately. Our staff will review this information with the participant at each weekly visit and we will supplement pill counts with the ACTG Interview of Antiretroviral Medication Use which was developed by the Adult AIDS Clinical Trials Group to assess in detail HIV medication adherence over the previous four days and takes about 10 minutes to complete [83]. The measure was modified for the current study to assess adherence to TOP. Side effects will be collected weekly using a checklist of 18 common AE's associated with TOP as indicated in the FDA-approved labeling for TOP [12].

Cannabis assessment (frequency and use): A single item assessing frequency of use for different forms of cannabis. To better assess for participants' cannabis use.

The DTS (Simons & Gaher, 2005) is a 15-item self-report measure that assesses the ability to experience and tolerate aversive emotional states using a Likert type scale (1= Strongly Agree to 5 = Strongly Disagree). Specifically, the DTS measures the tolerance of aversive emotional states, appraisal of distress, attention absorbed by distress, and efforts to regulate distress. The DTS displays good internal consistency, convergent and discriminant validity, and temporal stability.

Medication Adherence form: A 2 item questionnaire regarding medication adherence

Coronavirus Stressor Survey - This survey will be used to determine stressors patients face during the coronavirus pandemic. This assessment will be given at all assessment timepoints. (McLean, C. P. & Cloitre, M., 2020).

COVID Impact on Therapy Participation survey - This survey is meant to measure how COVID-19 has impacted participants ability to participate in evidence-based psychotherapy research at the VA.

Section 9.9 Data Safety Monitoring Board or Plan

9.9) Provide a Data Safety Monitoring Plan (DSMP) or the details of a Data Safety Monitoring Board.

Data Safety Monitoring (DSM). DSM will include periodic review and reporting of participant accrual, adverse event rates, treatment compliance, and drop-out rates. Study termination will be triggered by excessive drop-outs or adverse events. Adverse events includes 1) need to break confidentiality, 2) loss of data, 3) inadvertent harm caused by study participation, 4) patient suicidality. If treatment is needed during the follow-up phase due to increased alcohol consumption or serious psychiatric/medical symptoms, patients will be referred to appropriate treatment and followed by the PIs and study therapist until treatment is initiated. Adverse events will be reported to the San Diego VA's IRB and the VA ORD (serious adverse events within 48 hours) and clinically managed as appropriate. A summary of all adverse events will be submitted to VA ORD and RR&D annually. The PI (licensed in the state of California) will be available by phone 24-hours a day. The PI will be responsible for initial determination of serious adverse events from non-serious adverse events. This study would report to the VA DSMB and follow all criteria for reporting.
An Adverse Event (AE) is any unexpected medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. This includes any clinical or laboratory change that does not commonly occur in that participant and is considered clinically significant. All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be recorded throughout the study. The study physician will also be responsible for determining causal relationship between the study treatment and all AEs. Withdrawal from the study as a result of an AE or of therapeutic measures taken to treat an AE shall be at the discretion of the study clinicians. If a participant withdraws from the study for any reason, the study team will follow all participants with any ongoing AE until the AE is resolved or until it is deemed stable.
FDA 21CFR312.32 defines a serious adverse drug experience (SAE) as any adverse drug experience occurring at any dose that results in any of the following outcomes: death; a life threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse experiences when, based on appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes in this definition. The judgment of whether a particular AE meets the above criteria for an SAE shall be at the discretion of Dr. Norman.
It will also be the responsibility of Dr. Norman to document all SAEs and/or make referrals for appropriate care. All SAEs will be reported to the IRB, within 48 hours of their discovery. The blind can be broken at any point throughout the study as needed to protect participants' safety. Dr. Norman will meet with the research staff on a weekly basis to discuss study progress and potential problems, and will review collected data weekly, to ensure compliance with study protocols and data integrity. She will convene monthly meetings of investigators and project staff to ensure high levels of communication within the study team.
Participants in need of additional services. A plan is in place for identifying and referring individuals who report suicidality, either through self-report on assessment measures (e.g., PHQ-9 C-SSRS), or during a clinical contact. Participants identified as at imminent risk will be further evaluated by the site PI or, if needed, escorted to the emergency services at the VA. If indicated, referrals for treatment will be provided. In our ongoing trials, we have used this procedure and have provided referrals for both alcohol use and mental health treatment.

Section 9.10 Laboratory Tests

9.10) For each research laboratory test (not lab tests used as part of standard care), identify the test and indicate if the test results will or will not be used clinically for diagnosis, treatment, or prevention of disease. *Please note, only results from properly accredited laboratories can be used for diagnosis, treatment, and prevention of disease*.

DNA extraction and genotyping:
o We will utilize the VMRF CFAR genomics core and standard extraction from Oragene salivary samples and polymerase chain methods as previously described by (Kolassa et al. 2010; Valente et al. 2011a) for genotyping. Genotype frequencies will be tested against Hardy Weinberger Equilibrium using Pearson's goodness of fit $\chi 2$.

Section 9.11 Pictures and Audio/Video Recordings of Patients

9.11) Describe the purpose and of photographs (facial) or audio or video recordings of patients

Audio Recordings: All therapy sessions as well as select assessments will be audio-recorded. Study therapists and Assessors will receive weekly feedback and supervision on their skillfulness and adherence to treatment guidelines using review standards developed by Carroll et al. and refined in our lab [61].Audio recordings will only be reviewed for supervision, reliability, and treatment adherence purposes, and recordings will be erased as soon as data are analyzed.
All treatment sessions and interviews will be recorded on digital audio recorders "Sony ICD-UX533""Sony ICD-PX333", "Olympus VN-1800", "Olympus VN-6200PC", "Olympus Vn-7200", "Olympus DP-201 and the "Olympus VN-6300pc" or other VA approved recording technology. All recordings will be placed on the VA server behind the VA firewall. Audio recordings will be reviewed by study investigators, and a random sample will be selected for reliability, and treatment adherence purposes.

Section 10 - Human Subjects

10) Describe the characteristics of the proposed subject population. Include age, gender, ethnicity, and health status as appropriate. Provide inclusion and exclusion criteria as appropriate. Indicate the number of VASDHS participants to be studied. For multisite studies, also provide the total number of subjects from all sites. Indicate the estimated number of consented subjects that will fail the screening process, if any.

Protection of Human Subjects
1. Risks to the Subjects.
1.a. Human Subjects Involvement and Characteristics
The participants in this study will be 120 outpatient male and female Veterans (60 per treatment condition), ages 18 or older, with alcohol use disorder (AUD) and PTSD.

In order to ensure that our sample represents the diversity of comorbidity in Veterans with PTSD, exclusion criteria are minimized and include only those factors that contraindicate primary treatment for PTSD, prevent the Veteran from benefiting from the current program, or may interfere with the mechanisms under study.

Inclusion criteria are:
1) Veterans of the U.S. military and/or Reserve/National Guard members,
2) at least 18 years of age,
3) survivors of a psychological trauma meeting DSM-5 criterion A, and are at least one month post-trauma,
4) have current DSM-5 diagnoses of AUD and PTSD based on semi-structured diagnostic interviews,
5) have at least 20 days of heavy drinking (>= 5 drinks/day for men and >= 4/drinks per day for women) in the last 90 days spent in a non-restricted environment and meet criteria for heavy drinking at least 4 days in the last 30 days prior to screening,
6) are not currently receiving trauma-focused psychotherapy,
7) are literate in English and intend to stay in the San Diego area during the study,
8) are willing to attend psychotherapy, medication, and assessment sessions,
9) trying or planning to try to cut down on or abstain from alcohol,
10) for females of childbearing potential, agree to use an approved form of contraception for the duration of the study, including hormonal contraceptives (e.g., oral contraceptives or implantable devices), intrauterine device (IUD), or double barrier methods (e.g., diaphragm with spermicidal condom); barrier method is preferred as topiramate may make birth control less effective,
11) Individuals with clinically significant renal disease and/or impaired renal function, as defined by clinically significant elevation of blood urea nitrogen (BUN) or creatinine or an estimated creatinine clearance of < 60 mL/min, can be included with physician approval, however the dosing schedule and maximum dose will be adjusted in accordance with FDA prescribing guidelines,
12) if individual is on another addiction medication, they should be on a stable approved addiction medication dose (at least two weeks before starting study drug) throughout the study,
13) are capable of giving informed consent.

Exclusion criteria are:
1) Subjects known to have clinically significant unstable medical or psychiatric conditions, where participation is deemed by investigators and study physicians to be risky, including but not limited to:

-AST and/or ALT >5 times the upper limit of the normal range and/or an increased serum bilirubin >2 times the upper limit of normal.
-Seizure disorders
2) have been treated with Topiramate for any reason in the past and discontinued the drug due

to hypersensitivity reaction
3) in the opinion of the investigator, should not be enrolled because of the precautions, warnings, or contraindications listed on the Topiramate package insert, (e.g., certain types of glaucoma),
4) are pregnant, lactating, or plan to become pregnant during the period of participation in the study
5) in the judgment of the investigator, represent a significant risk of suicidal or homicidal behavior

Women and Minorities
Women comprise 11% (e.g., SAMI clinic) to 60% (Military Sexual Trauma clinic) of the Veterans seen in the clinics from which we will be recruiting, and approximately 24% of Veterans in the program are minorities. Consistent with SAMI demographics as a whole, 10% of participants in our current Merit study over the past 3 years have been women. We have been able to obtain 26% Hispanic, 16% African American, and 20% other ethnic groups, for a total of 52% from minority groups. We will continue attempts to oversample these groups to obtain adequate recruitment of females and minorities to examine effect sizes for these groups relative to male and Caucasian counterparts.
1.b. Sources of Materials: The data relevant to the proposed project will be gathered strictly for research purposes. Blood and urine specimens obtained are for clinical and research purposes only. Sources of research data will be demographic data collected from participants recruited for this study, ratings from independent clinical evaluators, patient self-reports, toxicology screens, and through VA CPRS chart review.

Section 10.6 Verification of non-pregnancy

10.6) To include women of child bearing potential but exclude pregnant women, indicate how it will be determined that the women are not pregnant:

Women that are pregnant , lactating, or plan to become pregnant during the period of participation in the study will be excluded from participation. All eligible participants will receive a laboratory diagnostic evaluation consisting of a chemistry panel, complete blood count, liver function tests (LFTs), urine toxicology screen and pregnancy test during their screening and/or randomization appointments so that participants with any illnesses that might adversely be affected by their participation in the trial will be excluded.

Section 11 - Recruitment

11) Describe the plans for recruitment of subjects (or selection of subjects as in record review). This description must include how, when, and where potential subjects are approached as well as procedures such as data mining, physician referral, etc. Include how selection is equitable. Indicate if vulnerability to coercion may be present and if so plans to ensure voluntary participation.

Recruitment Methods. Potential participants will contact our study in response to 1) flyers posted in VA mental health, primary care, and alcohol and substance use treatment programs; 2) advertisements in print and web-based media; 3) referrals from VA primary care, ADTP/SAMI, PTSD, and other psychiatry clinics and 4) from other research studies who's participants agreed to be re-contacted. We plan to recruit 3-4 participants per month for this study. Following verbal consent, potential participants will undergo either an in-person screening or a phone screening that takes approximately 30-45 minutes to complete. The screening, used in the PI's current CSR&D merit study, is intended to detect clinically significant alcohol use and PTSD symptoms. It consists of screening items from the SCID [52] and the PCL-5 [53] for disorders that are part of the inclusion and exclusion criteria. Study staff will review their CPRS record to determine if there are any exclusion criteria that was not disclosed in the screening before eligibility is determined. Those who meet study criteria will attend an in-person interview where they will sign informed consent documents and take part in a baseline assessment. Following baseline assessment, participants will be randomized to the intervention or control condition.

In regards to specific VA clinic recruitment (3) Erika Blanes, Project coordinator is part of the SAMI clinic and has access to all ADTP/SAMI CPRS consults. In an effort to provide veterans with more treatment options, she will review all consults to ADTP/SAMI for eligibility for this research study. Those who meet study criteria after record review will be presented information about the research study in the SAMI evaluation group, and provide a "Consent to Contact" form that gives

research staff permission to contact the Veteran to describe the study and details of study participation. Based on chart review, intake diagnostic interview, and staff consensus, if appropriate, the veteran will be scheduled for a consent and baseline assessment. As with our prior Merit studies, study interventions will be delivered within the SAMI program. Laura Westendorf and Julia Katawazi will provide back up assistance to Erika Blanes as needed for recruitment in these clinics.

Veterans referred to the PTSD Clinical Team or MST services at the San Diego VA will have the study described to them during orientation group by one of the group leaders and be provided a "Consent to Contact" form that gives research staff permission to contact the Veteran and describe the study and details of study participation. Interested Veterans will have the opportunity to meet with the study coordinator to discuss participation. Veterans who sign the consent to contact form will have their CPRS record reviewed prior to determining eligibility to insure there is no exclusion criteria noted on their record. If appropriate, they will be scheduled for an in-person screening to determined eligibility.

In regards to recruitment from other research studies, we will collaborate with Dr. Sonya Norman's "Integrated Alcohol Disorder and PTSD Treatment" protocol number H130080 and "Effectiveness of evidence based treatments for PTSD symptoms and trauma-related mental health problems among Veterans" study protocol number H130296. For veterans who agreed to re-contact, study staff will first review their CPRS record to determine if there are any exclusion criteria prior to contacting the veteran to ensure there are no immediate exclusion criteria that would make the veteran ineligible. Veterans who are recruited through these studies who did not have any indication of exclusion criteria in their CPRS record and who have agreed to be re-contacted about other research, will be contacted by letter and/or phone after record screen if no immediate exclusion criteria are found. If the participant did not agree to initial contact by phone, a letter will be sent first. After a period of 2 weeks if a letter is sent, and if no contact is made by the veteran, study staff will follow up by phone to provide the veteran with more information about the study. If participants are interested, they will be scheduled for an in-person or telephone screening session to determine eligibility.

fMRI
Participants will be asked if they are interested to take part in the optional fMRI study titled "Neuromarkers of Treatment for Comorbid Posttraumatic Stress Disorder and Alcohol Use Disorder IRB # H170116 (P.I. Andrea Spadoni-Townsend, PhD). If participants consent to be contacted for the optional study, Dr. Spadoni-Townsend's approved research team will contact patient and if patient agrees they will consent them for the study. (see recruitment for protocol H170116)

Section 11.1 Recruitment Materials

11.1) Identify all recruitment materials (flyers, advertisements, letters, etc.) that will be used. The text of all communications with prospective participants must be reviewed and approved by the IRB before it can be used. You will be reminded to attach copies of recruitment materials to the initial submission packet.

Flyers and brochures will be available to interested participants and posted in various locations thought the VA. Advertisements in both print and web-based media will be used for recruitment.

Section 12 - Informed Consent

12) Indicate whether or not each category of consent is involved in this study:

12a) **Signed** informed consent

(•) Yes ( ) No

12b) Signed consent for **picture/voice recording** (VA form 10-3203) [NO LONGER REQUIRED]

(•) Yes ( ) No

12c) Waiver of documented consent (e.g., **oral** consent)

( ) Yes (•) No

12d) Request for a **waiver** of consent (i.e., a "full" waiver, not just for screening)

○ Yes ◉ No

12e) Alteration of **other required elements** of consent.

○ Yes ◉ No

12f) **Child** assent to participate (Director approval will be required)

○ Yes ◉ No

12g) Will any language **other than English** be used by those obtaining consent and understood by the prospective participant or the legally authorized representative?

○ Yes ◉ No

12h) **Decisional Capacity Assessment** to determine if participants have the capacity to consent for themselves.

○ Yes ◉ No

12i) **Surrogate** consent (legally authorized representative)

○ Yes ◉ No

Section 12.1 Informed Consent Process

12.1a) Will consent be obtained before any study procedures are performed (including screening procedures except screening procedures with Consent/HIPAA waiver approval)?

◉ Yes ○ No

12.1b) Will the information being communicated to the participant or legally authorized representative during the consent process include exculpatory language through which the participant or legally authorized representative is made to waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the VA or its agents from liability for negligence.

○ Yes ◉ No

12.1c) A master list of all VA subjects consented (written or not) under this protocol number will be maintained. (If a waiver of the master list entry requirement is requested below and will be approved, indicate Agree).

◉ Agree ○ Disagree

12.1d) Identify the circumstances under which consent will be obtained including where the process will take place; any waiting period between describing the research and obtaining consent including sufficient time for the prospective participant to consider participation, and any steps taken to minimize the possibility of coercion or undue influence.

After the veteran completes the screening, the project coordinator will discuss the results with the PI as soon as possible. This will also provide the veteran time to review the requirements of the study and their interest in participating. If it is determined that the veteran is eligible for the study, they will be scheduled for a consent and intake appointment. Consenting will take place in a private room in the VA Hospital which will take approximately 45 minutes – 1 hour. Immediately following consent, the veteran will complete their intake assessment which can take around 5 hours.

Enrollment appointments can also be scheduled using VA approved secure Telehealth communication software or telephone. We will send an encrypted email (using VA Azure RMS), a

message through MyHealtheVet and/or send documents by US mail containing (1) the approved ICF, (2) the approved HIPAA document, (3) the CA Experimental Subjects Bill of Rights, and (4) fillable PDF baseline assessment documents, and arrange a telehealth or through VA approved secure Telehealth communication software to complete the informed consent process, explain the HIPAA Authorization, and CA Experimental Subjects Bill of Rights. If the visit is completed by VA approved secure Telehealth communication software, the staff member will witness the signing of the ICF and HIPAA Authorization and will instruct the potential participant to provide documentation of written informed consent by one of the following methods: (1) returning images of the documents through MyHealtheVet, (2) by allowing a screenshot of the signed documents (approval date and signature must be clearly visible), (3) study staff can have the participant digitally sign the fillable PDF documents which can be saved directly to the R Drive, (4) or document can be signed and returned via encrypted email (using VA Azure RMS) (5) documents can be sent and signed via DocuSign. If documents were mailed, the patient will be instructed to mail back the signed documents. If documents were mailed, the patient will be instructed to mail back the signed documents. These electronic documents will be stored electronically separate from study data on the R: drive. Paper documents will be stored securely according to VA requirements.

If the visit is done by phone, the (1) the approved ICF, (2) the approved HIPAA document, (3) the CA Experimental Subjects Bill of Rights, and (4) baseline assessment documents will be emailed (using VA Azure RMS and the participant will need to print all documents) and/or hard copied will be mailed to the participant. Study staff will call the participant at the scheduled appointment time to complete the documents. Study staff along with the participant will complete the informed consent document, explain the HIPAA Authorization, and CA Experimental Subjects Bill of Rights. The participant will be instructed to mail back the signed consent and HIPAA forms. Once the forms are received by study staff, the baseline assessments will be scheduled and completed by phone or through VA approved secure Telehealth communication software.

Participants will be sent a copy of the signed and dated forms, regardless if the Informed Consent appointment was completed by VA approved secure Telehealth communication software, by phone, or in person.

The veteran will be reminded that their consent must be given freely and that their VA benefits will not be affected should they choose not to participate or if they drop out of the study. The veteran is free to stop participation in the study at any time for any reason.

Section 12.9 HIPAA Authorization

For each category below, indicate whether or not this study involves the indicated process:

12.9a) **Signed** HIPAA Authorization

(•) Yes ( ) No

12.9b) HIPAA/consent waiver or alteration for **screening** purposes only

(•) Yes ( ) No

12.9c) Full HIPAA **waiver** or alteration

( ) Yes (•) No

12.9d) HIPAA **Authorization** or waiver is **not required** for some or all of the study subjects (e. g. no health data)

( ) Yes (•) No

Section 12.10 HIPAA Waivers and Alterations

12.10a) Describe the purpose/nature of the HIPAA waiver or alteration and list specifically, what identifiers and health information are being requested under the waiver/alteration and identify whether the waiver is for access, use, and/or collection of this information.

For potential participants that call in from the flyers/brochures/websites, those that are referred from VA clinics and those who are recruited through re-contact list from other research studies, we will request a partial waiver of HIPAA Authorization for screening. Study staff will review their CPRS record to determine if there are any exclusion criteria prior to the in-person screening to ensure there are no immediate exclusion criteria that would make the veteran ineligible (name and last 4 of SS# will be requested). If the participant is eligible based on their CPRS record findings and they are interested participating, they will be scheduled for an in-person screening. If participants are deemed to be ineligible after the in-person screening, then all information, including their responses will be shredded. If participants are eligible after the in-person screening, they will be scheduled for an in-person consent where Subject's Bill of Rights will be given, informed consent (VA form 10-1086) and HIPAA will be completed followed by a baseline assessments. The nature of the study will be explained, portions repeated as necessary, and questions answered.
Participants who are recruited through VA clinics will be offered the option of study involvement via their clinicians at standard appointments (i.e., orientation session, intake appointment, regular psychotherapy/medication appointments). Interested participants will give their clinician either their verbal consent to be contacted regarding the study, and their information will be given to the study coordinator, via a CPRS note, or the Research Contact Form to complete with their contact information which will be given to/collected by the study coordinator or a flyer about the study, with the study coordinator's information

12.10b) The use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals.

◉ Agree ○ Disagree

12.10c) The plan to protect the identifiers from improper use and disclosure is adequate.

◉ Agree ○ Disagree

Describe the plan

Hard copy data will be collected by approved research staff and stored with other sensitive information according to the data security plan. Full HIPAA forms will be signed along with the consenting process

12.10d) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law (VA Records Control Schedule does not currently permit destruction)

◉ Agree ○ Disagree

12.10d2) Describe the plan

Data will only be destroyed according to RCS-10 under Records Control Manager guidance.

12.10e) By signing this protocol for submission, the PI is providing written assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by the Privacy Rule. 38 U.S.C. 7332 Information: If the waiver of HIPAA authorization is for the use of 38 USC 7332 information (applicable to drug abuse, alcohol abuse, HIV infection, and sickle cell anemia records), by signing this protocol for submission the PI is providing written assurance that the purpose of the data is to conduct scientific research and that no personnel involved may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner. (Ref: 38 U.S.C. 7332(b)(2)(B))

◉ Agree ○ Disagree

12.10f) The research could not practicably be conducted without the waiver or alteration

◉ Agree ○ Disagree

12.10f2) Describe how the waiver/alteration enables the research to be conducted

The HIPAA waiver enables study to be conducted because by reviewing patients CPRS records we will be able to determine if there are any exclusion criteria prior to the in-person screening to ensure there are no immediate exclusion criteria that would make the veteran ineligible (name and last 4 of SS# will be requested). If the participant is eligible based on their CPRS record findings and they are interested participating, they will be scheduled for an in-person screening. If participants are deemed to be ineligible after the in-person screening, then all information, including their responses will be shredded

12.10g) The research could not practicably be conducted without access to and use of the PHI

◉ Agree ○ Disagree

12.10g2) Describe why it would be impracticable to conduct this research without the PHI described 12.10a. (v3/8/18)

We request the use of PHI (name and last 4 of SS# will be requested) for screening purposes, appointment scheduling, and follow up (contact information), electronic payment as well as record review for inclusion exclusion criteria.

Section 13 - Alternatives to Participation

13) Describe the alternatives to participation in this research study (see ? for guidance)

Alternatives are to not participate in the study. All participants who do not wish to participate in the study or who are not eligible will complete the regular outpatient program at the VASDHS. Referrals to appropriate mental health services within VASDHS will be given if needed and/or requested.

Section 14 - Potential Risks

14) Describe any potential or known risks or discomforts and assess their likelihood and seriousness. (see ? for guidance)

Potential Risks: Potential risks associated with participation in the study are: 1) loss of confidentiality; 2) feeling uncomfortable during the assessment or therapy process either due to talking about trauma, emotional topics, or symptoms; 3) becoming more anxious, depressed, or developing suicidal thinking; 4) increasing one's alcohol or other illicit drug use; 5) therapeutic risks associated with Topiramate use; 6) discomfort, bruising, or other possible risks of venipuncture (inserting a needle into a vein to draw blood). Number 1 and 6 are research risks, number 2 is both a therapeutic and research risk; numbers 3, 4, and 5 are therapeutic risks; 7) The genetic testing portion of the study entails a small chance for loss of confidentiality which could affect employment or insurance. However, discrimination based on genetic information is now illegal.

Numbers 1), 6)and 7) are research risks, number 2) is both a therapeutic and research risk; numbers 3), 4) and 5) are therapeutic risks.

Section 15 - Risk Management

15) Describe the procedures for protecting against or minimizing any potential risks/discomforts, and the adequacy of resources for conducting the study and resources participants may need as a consequence of the research. See ? for further requirements.

The following steps will be taken to minimize the risk to confidentiality.
1) All data and saliva samples will be identified only with participant numbers, never with names or initials. All data will be stored in locked filing cabinets in offices at the VA or the PI's secure VA research folder in the VA research drive, and only study personnel will have access to the data. The list associating names and participant numbers will be stored in a locked cabinet separate from that in which other study data will be stored, and only the PI and project coordinator will have access to the key. Research staff will not release any information to anyone other than the

participant without that participant's consent. Participants will not be identified by name or other identifying features in any publication resulting from this research. Audio recordings will only be reviewed for supervision, reliability, and treatment adherence purposes and recordings will be erased as soon as data are analyzed.

2) To minimize the risk of patient discomfort, confidentiality will be stressed, participants will be offered breaks as needed, they will be informed that they have the right to refuse to answer questions or to terminate their participation in the study at any time without prejudice, and everyone who interacts with participants will be trained and supervised. Clinical staff will be available at each location if immediate in-person evaluation is required for medical or mental health issues.

3) and 4) To minimize the risk of patients becoming more anxious or depressed or increase drinking, every patient will be given a 24-hour contact phone number to call in the event of increased symptoms. During each assessment, the independent evaluator (IE) will assess for any major changes in health (e.g., overnight hospitalizations), possible adverse events, suicidal ideation, and general well-being. Study clinicians, during medication and psychotherapy visits, will assess for clinical worsening as part of the session protocols. If worsening symptoms are detected at any visit, a study clinician will be available to evaluate the patient and refer to appropriate treatment if needed. When in doubt, the decision whether continued participation in the study is safe and clinically warranted will always be on the side of patient safety. If a therapist or assessor identifies worsening substance use, the study investigators will evaluate whether best clinical care indicates a need for continuation in the study or more intensive SUD treatment. Participants will complete the Substance Use Inventory (SUI) at each session which will show worsening substance use. Therapists will be trained to contact the PI if a participant reports three or more days per week of alcohol use with more than four standard drinks or three or more days of illicit drug use in a week. If more intensive treatment is appropriate, we will assist the participant in obtaining the appropriate treatment. If the treatment is counter to study criteria, then we will discontinue the participant from the study following a final evaluation.

Adverse events, including those unlikely to be the result of participation in the research (e.g., hospitalization due to an automobile accident), will be monitored at every study contact, including medication, psychotherapy and assessment visits. They will be reported to the appropriate human subjects committees as per policy.

There is always a risk associated with the management of patients with AUD or PTSD that they will develop suicidality. This risk will be carefully mitigated by the systematic and careful assessment of suicidality throughout the protocol. This will be carefully done via the assessment measures to be completed by the participants, in-session assessments made by the therapists, and through comprehensive suicide risk assessments that are part of standard VA care. Participants who develop suicidality will be evaluated by a study clinician and investigators to determine whether continued participation in the study is safe and clinically warranted. If the study personnel and participant feel that treatment not allowed in the protocol is indicated (e.g., a different form of medication or psychotherapy, or hospitalization), an endpoint evaluation will be done, the participant will be discontinued from the study, and the participant will be referred for appropriate treatment.

5) Participants will be informed of the risks associated with the use of Topiramate, including all clinically significant warnings provided by the manufacturer in the medication package insert. This includes all current warnings and cautions in the most recent FDA guidelines dated May 2019 [95]. Given our frequent monitoring and standardized assessment of mood changes, we are already in compliance with the FDA's recommendation to monitor for this potentially rare adverse event. Participants will be informed that, as with any drug, Topiramate administration may involve other risks that are not known at the present time. If the study staff learns of any new possible risk or side effects of this drug, participants will be notified immediately. Participants will be informed that their condition may remain the same or deteriorate due to an ineffective treatment. They will also be informed of the availability of alternative treatments to facilitate alcohol use reduction. Participants will be told that if, in the opinion of the doctor, there are problems caused by their participation in the study that make it unwise for the participant to continue, their participation will be stopped. Patients who are discontinued from the study for any reason will be given a referral for further treatment if indicated.

All eligible participants will receive a laboratory diagnostic evaluation consisting of a chemistry panel, complete blood count, liver function tests (LFTs), urine toxicology screen and pregnancy test during their screening and/or randomization appointments so that participants with any illnesses that might adversely be affected by their participation in the trial will be excluded.

6) The risks of simple venipuncture commonly include the occurrence of discomfort and/or bruising at the site of the puncture. Less commonly, fainting, the formation of a small blood clots or swelling of the vein and surrounding tissue, or bleeding from the puncture site may occur.

There could be infection at the site where the blood was drawn. All blood draws will occur at the VA lab by certified professionals.

Additional safety measures are as follows: 1) we will recruit individuals with AUD/PTSD who are seeking treatment to reduce alcohol use and symptoms; 2) a careful intake assessment will be conducted and patients in need of immediate psychiatric treatment for severe depression or other conditions will not be enrolled and provided referrals; 3) our team consists of clinicians with extensive experience in the treatment of patients with AUD and PTSD; 4) study therapists will review all active cases weekly with the PI and therapy supervisor, and all members of the research team will immediately communicate any health or psychiatric-related problems to the PIs who will ensure that necessary safety steps are implemented; and 5) participants who are discontinued from the study will be scheduled for a final evaluation within one week and given appropriate treatment referrals. Participants discontinued due to a serious adverse event will be followed clinically by medical staff until the adverse event is resolved or becomes stable. Reasons for discontinuation and referrals made will be documented in the participants' casebooks.

Psychiatric Emergencies
If exacerbation of psychological symptoms occurs, members of the research team will discontinue assessment and assist the subject to access care.

Telephone assessments - All risk management and emergency response procedures would be followed in accordance with the protocol and we will use all procedures to mitigate risk when talking with a participant by phone during screening or scheduling appointments. In an effort to decrease risks associated with telephone screening, the veteran will be given the information to the nearest VA Health Center to their new residence and a licensed clinical psychologist will be available over the phone for crisis counseling if such an even should occur during any research procedure for the study.

Section 16 - Privacy and Confidentiality

16a) Provide a brief description of how participant privacy and confidentiality will be protected in this study.

Only approved study personnel will have access to study data, and all study personnel have been trained regarding privacy and security issues. In the event of a real or suspected breach of security, the VA Police, the VA Information Security Officer, and the VA Privacy Officer will be notified. Secure information will be accessed, stored, and destroyed according to a data security plan that will promote security and privacy, including, but not limited to the following:

Identifiers will be removed from study data following guidelines outlined by VA Handbook including 1605.1 Appendix B. We will assign Veterans a study identification number unrelated to identifying information. We will create a master list linking the study identification number to the Veteran record. The master list will be maintained by the Principal Investigator and stored in a locked cabinet in her laboratory. Access to the master list will be limited to the P.I. and her designees, all of whom will have completed VA IRB training requirements.

We will create and maintain a separate password-protected electronic study database containing the study identification number and study data specified above as well as genotype data from salivary samples. Individually identifiable health information (IIHI), as defined by Health Insurance Portability and Accountability Act of 1996 (HIPAA, Title II) will not be included in the study database. Specifically, we will exclude the 18 elements outlined by the Privacy Rule of HIPAA (section 164.514 and VA Handbook 1605.1 Appendix B) and "safe harbor" definition. Social security numbers will only be used to look-up medical records, and will not be maintained as data. Further, we will make all necessary efforts to insure a Veteran may not be identified via extraction of any combination of the data maintained in the study database in which identifiers have been removed. Access to the study database will also be limited to the P.I. and her IRB trained designees.

Electronic VASI
Audio Recordings: All treatment sessions and interviews will be recorded on digital audio recorders "Sony ICD-UX533", "Sony ICD-PX333","Olympus VN-1800", "Olympus VN-6200PC", "Olympus Vn-7200", " Olympus DP-201 and the "Olympus VN-6300pc" will be used in this study and placed on VA service for potential review by supervisors. These recorders will be stored in a locked cabinet in bldg. 1,room 2341. The audio recordings will be downloaded to the VA R:\drive. Copies of randomly selected interviews will be reviewed by Dr. Sonya Norman, who is a VASDHS employee and can review the information without removing it from VA grounds. Recordings will

be destroyed in accordance with the most current VA Records Control Schedule guidelines and in consultation with the VASDHS ISO and VASDHS IT Department Personnel.

In the event of a suspected security breach, we will notify the VA Privacy Officer, VA Police, and VA Information Security Officer.
Refer to the VA Privacy and Data Security Plan for further detail.

16a2) See Privacy and Data Security Plan for further details.

(•) Yes ( ) No

16b) Is SSN used for any purpose other than scanning Consent/HIPAA into the medical record? (e.g., subject payments, use of clinical record)

(•) Yes ( ) No

16b2) If YES, indicate purpose and justification:

Social security numbers will only be used for use of clinical records, or subject payments and will not be maintained as data. Further, we will make all necessary efforts to insure a Veteran may not be identified via extraction of any combination of the data maintained in the study database in which identifiers have been removed.

Section 16.1 Entry of CPRS Notes

16.1) Entry of a CPRS Research Informed Consent Note is required if any of the following apply:

- **The subject is admitted as an inpatient or treated as an outpatient for research**
- **The study involves research medical care or may affect medical care.**
- **The Informed Consent and HIPAA Authorization indicate notes will be entered**

Notes: Scanning the Consent and HIPAA Authorization into CPRS is no longer required. Linking the Consent to the Research Informed Consent Note is permitted (Unless the study has a Certificate of Confidentiality) and may be especially useful for trials involving the Research Pharmacy. · For Non-Veterans, if Research Informed Consent Notes are entered then the NOPP Acknowledgement must be scanned in. · A Research Progress Note should also be entered for each procedure or intervention. ·
Address the CPRS note requirement:

16.1a) Is entry of CPRS notes required based on the above criteria?

(•) Yes ( ) No

16.1b) Are CPRS notes entered?

(•) Yes ( ) No

16.1c) Is a CPRS waiver is requested instead?

( ) Yes (•) No

Section 17 - Potential Benefits

17) Discuss benefits that may be gained by the subject as well as potential benefits to society in general. (see ? for guidance)

The potential benefits for participants include decreased distress and alcohol use and improved quality of life. Study of the effectiveness of Topiramate and PE will also benefit individuals who have AUD and PTSD and society more generally by providing information about how best to treat co-occurring AUD and PTSD.

Section 18 - Risk/Benefit Ratio

18) Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

The potential benefits of improved understanding of how to manage patients with PTSD and AD outweighs the potential risks of this study.

Section 20 - Compensation for Participation

20) Provide all details and justifications of the compensation plan. See ? for detailed requirements.

Compensation. Participants will be compensated up to $230 for their time and effort for completing assessments: $40 baseline, $20 mid-treatment , $50 post-treatment, and $60 each post-treatment follow-up. Participants will complete the 2nd post treatment assessment interview and set of questionnaires 3 months after the 1st post treatment appointment. Participants will be scheduled for their 3rd and last post treatment interview 3 months after completing their 2nd post treatment assessment. Participants will be compensated $20 for DNA sample. Payments will be made directly to their bank accounts using electronic funds transfer when possible.

Section 21 - Responsibilities and Qualifications

Here are the identified study staff members

Sonya B. Norman, PhD

Abigail Candare Angkaw, PhD, Andrea Spadoni Townsend, PhD, Arthur L. Brody, MD, Brian Martis, MD, Brittany C Davis, Katharine I. Lacefield, PhD, Michelle Pitts, PhD, Murray B. Stein, MD, Scott Christian Matthews, MD, Victoria B. Risbrough, PhD, Julia G. Katawazi, Julie M. Holcomb, Kaitlyn E. Panza, PhD, Alexandra O. Higdon, PsyD, Jae Eun Park, Matthew T. Luciano, PhD, Morgan E. Marvin, BA, Ruth Klaming Miller, PhD, Alexander C. Kline, PhD, Alexandra Klein, PhD, Robert C. Lyons, PhD

21) Identify here by name those staff working on this protocol, unless they have no contact with subjects or identifiable data. Indicate their role and qualifications. Also indicate which of the study staff are authorized to obtain consent for subjects of VA research.

Sonya Norman, Ph.D. (Principal Investigator)-Dr. Norman will be responsible for oversight of all scientific, logistical and financial aspects of the study and for securing and maintaining appropriate approvals. She will coordinate the efforts of the Co-Investigators (Abigail Candare Angkaw, PhD, Arthur L. Brody, M.D., Brittany C Davis, PhD, Ryan Trim, PhD, Katherine Lacefield, PhD, Murray Stein, Scott Christian Matthews, Victoria Risbrough, PhD and Andrea Spadoni-Townsend, PhD, Brian Martis, MD., Michelle Pitts, PhD) and consultants and be responsible for hiring, training and supervising the study staff and overseeing supervision for the therapists.

Andrea Spadoni-Townsend, PhD is a co-investigator. She is the PI for the optional fMRI study titled " Neuromarkers of Treatment for Comorbid Posttraumatic Stress Disorder and Alcohol Use Disorder"; H170116. Participants who provide consent to contact on the consent form and are interested in hearing more about her study will be referred to her study staff.

All Investigators have the appropriate certifications and licenses to complete this study. Dr Norman will work with Dr. Matthews, (Co-I) Dr. Brody (Co-I) and Dr. Stein (Co-I) on the biomedical aspects of the study to complete data analyses and will author manuscripts.

Drs. Norman, Angkaw, Davis are privileged at the VA and are licensed psychologists in the state of California. Drs. Matthews, Brody, Martis and Stein are privileged at the VA and are licensed psychiatrist.

Drs. Matthews, Brody and Martis will provide psychiatry services for study participants.

Kaitlyn Panza, PhD, will serve as the primary recruiters and coordinators for the project under the supervision of Dr. Norman and the Co-Investigators. They will be responsible for daily research activities, including screening of potential study participants, recruitment, conducting

research assessments, training and supervising research assistants, and data management.

Julia G Katawazi, MA will be a Research Assistant with responsibilities for conducting research assessments and data entry. They are supervised by Dr. Norman.

Additionally, study therapists conducts individual psychotherapy interventions: Michelle Pitts, PhD., and Kaitlyn Panza, PhD, Alexander Kline, PhD, Matthew Luciano, PhD, and Alexandra Higdon, PhD.

Robert Lyons, M.S. is a Psychology graduate student in the San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology.

Ruth Klaming Miller, Morgan Marvin, Julie Holcomb, Alexandra Klein, Jae E Park will provide administrative research support.

Section 22 - Bibliography

22) List relevant articles that the IRB can use to provide necessary background for the protocol. Do not include an extensive NIH-grant-style bibliography. **(Up to 5 recommended, but use more if needed to support the protocol or citations above.)**

References

1. Foa, E.B., et al., Concurrent naltrexone and prolonged exposure therapy for patients with comorbid alcohol dependence and PTSD: a randomized clinical trial. Journal of American Medicine (JAMA), 2013. 310(5): p. 488-95.
2. VA/DoD, VA/DoD Clinical Practice Guidline Management of Substance Abuse Disorder (SUD). 2015.
3. Watts, B.V., et al., Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. The Journal of Clinical Psychiatry, 2013. 74(6): p. e541-50.
4. Ralevski, E., M. Taylor, and I. Petrakis, Pharmacotherapy and psychotherapy studies designed to treat alcohol use disorders and co-occurring PTSD: A Review. The American Journal of Drug and Alcohol Abuse, In press.
5. Blodgett, J.C., et al., A Meta#Analysis of Topiramate's Effects for Individuals with Alcohol Use Disorders. Alcoholism: Clinical and Experimental Research, 2014. 38(6): p. 1481-1488.
6. Del Re, A., et al., Prescription of topiramate to treat alcohol use disorders in the veterans health administration. Addict Sci Clin Pract, 2013. 8(1): p. 12.
7. Seal, K.H., et al., Substance use disorders in Iraq and Afghanistan veterans in VA healthcare, 2001–2010: Implications for screening, diagnosis and treatment. Drug and Alcohol Dependence, 2011. 116(1): p. 93-101.
8. Roberts, N.P., et al., Psychological interventions for post-traumatic stress disorder and comorbid substance use disorder: A systematic review and meta-analysis. Clinical Psychology Review, 2015. 38: p. 25-38.
9. Larsen, S.E., et al., Symptom exacerbations in trauma-focused treatments: Associations with treatment outcome and non-completion. Behaviour research and therapy, 2016. 77: p. 68-77.
10. Batki, S.L., et al., Topiramate Treatment of Alcohol Use Disorder in Veterans with Posttraumatic Stress Disorder: A Randomized Controlled Pilot Trial. Alcoholism: Clinical and Experimental Research, 2014. 38(8): p. 2169-2177.
11. Farook, J.M., et al., Topiramate attenuates the stress-induced increase in alcohol consumption and preference in male C57BL/6J mice. Physiology & Behavior, 2009. 96(1): p. 189-193.
12. McLean, C., Su, Y.J., and E.B. Foa, Mechanisms of symptom reduction in a combined treatment for comorbid posttraumatic stress disorder and alcohol dependence. Journal of Consulting and Clinical Psychology, 2015. 83(3): p. 655-661.
13. Sommer, B., E. Mitchell, and T. Wroolie, Topiramate: Effects on cognition in patients with epilepsy, migraine headache and obesity. Ther Adv Neurol Disord, 2013. 6(4): p. 211-227.
14. Foa, E.B., et al., Does imaginal exposure exacerbate PTSD symptoms? Journal of Consulting and Clinical Psychology, 2002. 70: p. 1022-1028.
15. Debell, F., et al., A systematic review of the comorbidity between PTSD and alcohol misuse. Social Psychiatry and Psychiatric Epidemiology, 2014. 49(9): p. 1401-25.
16. Ouimette, P., R.H. Moos, and J.W. Finney, PTSD treatment and 5-year remission among patients with substance use and posttraumatic stress disorders. Journal of Consulting and Clinical Psychology, 2003. 71(2): p. 410-414.
17. Tate, S.R., et al., Health problems of substance-dependent veterans with and those without trauma history. Journal of substance abuse treatment, 2007. 33(1): p. 25-32.
18. McDevitt-Murphy, M.E., et al., PTSD symptoms, hazardous drinking, and health functioning among U.S. OEF and OIF veterans presenting to primary care. Journal of Traumatic Stress, 2010. 23(1): p. 108-111.

19. Foa, E., E. Hembree, and B.O. Rothbaum, Prolonged exposure therapy for PTSD: Emotional processing of traumatic experiences therapist guide. 2007, New York, NY: Oxford University Press.
20. VA/DoD, VA/DoD Clinical Practice Guidelines: Management of Post-Traumatic Stress Disorder and Acute Stress Reaction. 2010.
21. Kessler, R.C., et al., Posttraumatic stress disorder in the National Comorbidity Survey. Archives of General Psychiatry, 1995. 52: p. 1048-1060.
22. Reynolds, M., et al., Trauma and post-traumatic stress disorder in a drug treatment community service. The Psychiatrist, 2011. 35(7): p. 256-260.
23. Driessen, M., et al., Trauma and PTSD in patients with alcohol, drug, or dual dependence: A multi center study. Alcoholism, Clinical and Experimental Research, 2008. 32(3): p. 481-488.
24. Jacobsen, L.K., S.M. Southwick, and T.R. Kosten, Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. American Journal of Psychiatry, 2001. 158(8): p. 1184-1190.
25. Drapkin, M.L., et al., Baseline functioning among individuals with posttraumatic stress disorder and alcohol dependence. Journal of substance abuse treatment, 2011. 41(2): p. 186-192.
26. Ouimette, P.C., P.J. Brown, and L.M. Najavits, Course and treatment of patients with both substance use and posttraumatic stress disorders. Addictive Behaviors, 1998. 23(6): p. 785-795.
27. Sartor, C.E., et al., Posttraumatic stress disorder and alcohol dependence in young women. Journal of Studies on Alcohol and Drugs, 2010. 71(6): p. 810-818.
28. Seal, K.H., et al., Substance use disorders in Iraq and Afghanistan veterans in VA healthcare, 2001-2010: Implications for screening, diagnosis and treatment. Drug and Alcohol Dependence, 2011. 116(1-3): p. 93-9101.
29. Stappenbeck, C.A., et al., The effects of alcohol problems, PTSD, and combat exposure on nonphysical and physical aggression among Iraq and Afghanistan war veterans. Psychological Trauma: Theory, Research, Practice, and Policy, 2014. 6(1): p. 65-72.
30. Coffey, S.F., et al., Trauma-focused imaginal exposure for individuals with comorbid posttraumatic stress disorder and alcohol dependence: revealing mechanisms of alcohol craving in a cue reactivity paradigm. Psychology of Addictive Behaviors, 2006. 20(4): p. 425-435.
31. Saladin, M.E., et al., PTSD symptom severity as a predictor of cue-elicited drug craving in victims of violent crime. Addictive Behaviors, 2003. 28(9): p. 1611-1629.
32. Coffey, S.F., et al., Exposure Therapy for Substance Abusers with PTSD Translating Research to Practice. Behavior Modification, 2005. 29(1): p. 10-38.
33. Foa, E.B., et al., Processing of threat-related information in rape victims. Journal of Abnormal Psychology, 1991. 100(2): p. 156-162.
34. Foa, E.B., et al., Randomized trial of prolonged exposure for posttraumatic stress disorder with and without cognitive restructuring: outcome at academic and community clinics. Journal of Consulting and Clinical Psychology, 2005. 73: p. 953-964.
35. Rauch, S.A., et al., Prolonged exposure for PTSD in a Veterans Health Administration PTSD clinic. Journal of Traumatic Stress, 2009. 22(1): p. 60-64.
36. Institute of Medicine, Treatment of posttraumatic stress disorder: An assessment of the evidence. 2007: Washington, D.C.
37. Brown, P.J. and J. Wolfe, Substance abuse and post-traumatic stress disorder comorbidity. Drug and Alcohol Dependence, 1994. 35(1): p. 51-59.
38. Dansky, B.S., K.T. Brady, and M.E. Saladin, Untreated symptoms of PTSD among cocaine-dependent individuals: Changes over time. Journal of Substance Abuse Treatment, 1998. 15(6): p. 499-504.
39. Schnurr, P.P., et al., Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. JAMA, 2007. 297: p. 820-830.
40. Johnson, B.A., et al., Topiramate for treating alcohol dependence: a randomized controlled trial. The Journal of American Medical Association, 2007. 298(14): p. 1641-1651.
41. Arbaizar, B., et al., Topiramate in the treatment of alcohol dependence: a meta-analysis. Actas Esp Psiquiatr, 2010. 38(1): p. 8-12.
42. Petrakis, I.L., A Commentary on Topiramate Treatment of Alcohol Use Disorder in Veterans with PTSD: A Randomized Controlled Pilot Trial. Alcoholism: Clinical and Experimental Research, 2014. 38(8): p. 2167-2168.
43. Mozhui, K., et al., Strain differences in stress responsivity are associated with divergent amygdala gene expression and glutamate-mediated neuronal excitability. The Journal of Neuroscience, 2010. 30(15): p. 5357-5367.
44. Norman, S.B., E. Schmied, and G.E. Larson, Predictors of continued problem drinking and substance use following military discharge. Journal of Studies on Alcohol and Drugs, 2014. 75 (4): p. 557-66.
45. Tate, S.R., et al., Context of relapse for substance-dependent adults with and without comorbid psychiatric disorders. Addictive Behaviors, 2004. 29(9): p. 1707-1724.
46. Norman, S.B., et al., Development of the PTSD-alcohol expectancy questionnaire. Addictive Behaviors, 2008. 33(6): p. 841-847.
47. Norman, S.B., et al., Maximizing the utility of a single site randomized controlled psychotherapy trial. Contemporary clinical trials, 2015. 42: p. 244-251.
48. Norman, S.B., et al., Prolonged Exposure With Veterans in a Residential Substance Use

Treatment Program. Cognitive and Behavioral Practice, 2016. 23(2): p. 162-172.
49. Larson, G.E. and S.B. Norman, Prospective prediction of functional difficulties among recently separated Veterans. J Rehabil Res Dev, 2014. 53(1): p. 415-27.
50. Norman, S.B., et al., Student Veteran perceptions of facilitators and barriers to achieving academic goals. Journal of Rehabilitation Research & Development, 2015. 52(6): p. 701-713.
51. Schulz, K.F., D.G. Altman, and D. Moher, CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine, 2010. 8(1): p. 1-9.
52. First, M., et al., Structured Clinical Interview for DSM-5 Disorders–Research Version (SCID-5-RV). Arlington: American Psychiatric Assocation, 2014.
53. Weathers, F., et al., The PTSD Checklist for DSM-5 (PCL-5). Scale available from the National Center for PTSD (online), 2013.
54. Riggs, D.S. and E.B. Foa, Treatment for co-morbid posttraumatic stress disorder and substance use disorders, in Anxiety and Substance Use Disorders. 2008, Springer. p. 119-137.
55. Arnone, D., Review of the use of Topiramate for treatment of psychiatric disorders. Annals of General Psychiatry, 2005. 4(1): p. 1-14.
56. Likhitsathian, S., et al., Cognitive changes in topiramate-treated patients with alcoholism: a 12-week prospective study in patients recently detoxified. Psychiatry and Clinical Neurosciences, 2012. 66(3): p. 235-41.
57. Jonas, D.E., et al., Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD), Agency for Healthcare Research and Quality (US), Editor. 2013: Rockville, MD.
58. Mimrod, D., et al., A comparative study of the effect of carbamazepine and valproic acid on the pharmacokinetics and metabolic profile of topiramate at steady state in patients with epilepsy. Epilepsia, 2005. 46(7): p. 1046-54.
59. Bialer, M., et al., Pharmacokinetic interactions of topiramate. Clinical Pharmacokinetics, 2004. 43(12): p. 763-780.
60. Pettinati, H.M., et al., A structured approach to medical management: a psychosocial intervention to support pharmacotherapy in the treatment of alcohol dependence. Journal of Studies on Alcohol, Supplement, 2005(15): p. 170-178.
61. Carroll, K.M., et al., A general system for evaluating therapist adherence and competence in psychotherapy research in the addictions. Drug and Alcohol Dependence, 2000. 57(3): p. 225-238.
62. Perepletchikova, F. and A.E. Kazdin, Treatment integrity and therapeutic change: Issues and research recommendations. Clinical Psychology: Science and Practice, 2005. 12(4): p. 365-383.
63. Sobell, L.C. and M.B. Sobell, Timeline follow-back: a technique for assessing self reported alcohol consumption, in Measuring alcohol consumption: Psychological and Biochemical Methods, R. Litten and J.P. Allen, Editors. 1992, Humana Press: Clifton, NJ. p. 41-72.
64. Cahalan, D., I.H. Cisin, and H.M. Crossley, American drinking practices: A national study of drinking behavior and attitudes. Monographs of the Rutgers Center of Alcohol Studies. Vol. 6. 1969, New Haven, CT: College and University Press. 260.
65. McLellan, A.T., et al., The Fifth Edition of the Addiction Severity Index. Journal of Substance Abuse Treatment, 1992. 9(3): p. 199-213.
66. Weiss, R., et al., Weekly substance use inventory. Unpublished measure, Harvard University Medical School, Boston, MA, 1995.
67. Marlatt, G. and J. Gordon, Relapse prevention: Maintenance strategies in the treatment of addictive behaviors. 1985, New York, NY: Gilford Press.
68. Wills, T.A. and S. Shiffman, Coping and substance use. 1985, New York, NY: Academic Press.
69. Flannery, B.A., J. Volpicelli, and H. Pettinati, Psychometric properties of the Penn Alcohol and Craving Scale. Alcoholism: Clinical and Experimental Research, 1999. 23(8): p. 1289-1295.
70. Blake, D.D., et al., The development of a clinician#administered PTSD scale. Journal of Traumatic Stress, 1995. 8(1): p. 75-90.
71. Weathers, F.W., et al., PTSD Checklist for DSM-5 (PCL-5), National Center for PTSD, Editor. 2014: Boston, M.A.
72. Kroenke, K. and R.L. Spitzer, The PHQ-9: a new depression diagnostic and severity measure. Psychiatric Annals, 2002. 32(9): p. 509-515.
73. Posner, K., et al., Columbia-Suicide Severity Rating Scale (C-SSRS). 2008, The Research Foundation for Mental Hygiene, Inc: New York, NY.
74. Bovin, M. J., Black, S. K., Rodriguez, P., Lunney, C. A., Kleiman, S. E., Weathers, F. W., Schnurr, P. P., Spira, J., Keane, T. M., & Marx, B. P. (revise and resubmit). Development and validation of a measure of PTSD-related functional impairment: The Inventory of Psychosocial Functioning.
75. Marx, B.P., et al., Using the WHODAS 2.0 to assess functioning among veterans seeking compensation for posttraumatic stress disorder. Psychiatric Services, 2015. 66(12): p. 1312-1317.
76. Bastiaens, L., J. Galus, and M. Goodlin, The 12 Item WHODAS as Primary Self Report Outcome Measure in a Correctional Community Treatment Center for Dually Diagnosed Patients. Psychiatric Quarterly, 2015. 86(2): p. 219-224.
77. Mundt, J.C., et al., The Work and Social Adjustment Scale: a simple measure of impairment in functioning. The British Journal of Psychiatry, 2002. 180(5): p. 461-464.
78. Skevington, S.M., et al., The World Health Organization's WHOQOL-BREF quality of life

assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Quality of Life Research, 2004. 13(2): p. 299-310.
79. Nasreddine, Z.S., et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society, 2005. 53(4): p. 695-699.
80. Brandt, J. and R. Benedict, Hopkins Verbal Learning Test–Revised. Professional manual. 2001, Lutz, FL: Psychological Assessment Resources.
81. Devilly, G.J. and T.D. Borkovec, Psychometric properties of the credibility/expectancy questionnaire. Journal of Behavior Therapy and Experimental Psychiatry, 2000. 31(2): p. 73-86.
82. Larsen, D.L., et al., Assessment of client/patient satisfaction: development of a general scale. Eval Program Plann, 1979. 2(3): p. 197-207.
83. Chesney, M.A., et al., Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. AIDS care, 2000. 12(3): p. 255-266.
84. Little, R. and D. Rubin, Statistical analysis with missing data. 2nd ed. 2002, New York, NY: Wiley.
85. Schafer, J.L. and J.W. Graham, Missing data: our view of the state of the art. Psychol Methods, 2002. 7(2): p. 147-177.
86. Graham, J.W., et al., eds. Analysis with missing data in prevention research. The science of prevention: methodological advances from alcohol and substance abuse research, ed. K. Bryant, M. Windle, and S.A. West. 1997, American Psychological Association: Washington, DC. 325-366.
87. Collins, L.M., J.L. Schafer, and C.M. Kam, A comparison of inclusive and restrictive strategies in modern missing data procedures. Psychological Methods, 2001. 6(4): p. 330-351.
88. Little, R., Modeling the drop-out mechanism in repreated-measures studies. J Am Stat Assoc, 1995. 90: p. 1112-1121.
89. Hedeker, D. and R.D. Gibbons, Application of random-effects pattern-mixture models for missing data in longitudinal studies. Psychological Methods, 1997. 2(1): p. 64-78.
90. Singer, J.D. and J.B. Willett, Applied longitutindal data analysis: modeling change and even occurrence 2003, New York, NY: Oxford University Press.
91. Krull, J.L. and D.P. MacKinnon, Multilevel mediation modeling in group-based intervention studies. Evaluation Review, 1999. 23(4): p. 418-444.
92. Williams, J. and D.P. MacKinnon, Resampling and Distribution of the Product Methods for Testing Indirect Effects in Complex Models. Struct Equ Modeling, 2008. 15: p. 23-51.
93. Marx, B. P., Schnurr, P. P., Rodriguez, P., Holowka, D. W., Lunney, C. A., & Weathers, F. W. (2009, November). Development of a functional impairment scale for active duty service members and veterans. In K. M.Lester (Chair), Beyond PTSD symptom reduction: Social and health-related benefits of trauma focused treatment. Symposium conducted at the meeting for the International Society for Traumatic Stress Studies. Atlanta, GA.
94.Garin, O., et al., Validation of the" World Health Organization Disability Assessment Schedule, WHODAS-2" in patients with chronic diseases. Health and Quality of Life Outcomes, 2010. 8: p. 15-51.
95. U. S. Food and Drug Administration. (2019, May). Medication Guide and Full Prescribing Information for TOPAMAX (topiramate). (Reference ID: 4426133). Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020505s060,020844s051lbl.pdf

Section 23 - Sponsors and Collaborators

23) Clarify any industry financial or other support (e.g., NIH funds the study or Company X provides the assay kits). Identify non-VASDHS Research collaborators and their role in this protocol, including whether or not they have access to subjects or identified data.

Dr. Gregory Norman from the UCSD School of Medicine will provide statistical support. He will not have access to identifiable data.

If genotyping is conducted outside the VA it will be via approved VA vendors for this service with an MTA. DNA extraction will be conducted by CFAR, a VA affiliated core.

Section 24 - Biological Materials Transfer Agreement (BMTA)

24) Describe what material is transferred, the persons/institutions that send and receive the material, and the status of the BMTA for this purpose. (see ? for further guidance)

The material to be transferred is DNA from saliva samples collected under this protocol. If

genotyping is conducted outside the VA it will be via approved VA vendors for this service with an MTA. DNA extraction will be conducted by CFAR, a VA affiliated core.

Section 25 - Impact on Clinical Services

25) Which VA Clinical Services participate in the performance of the project? (NOTE: All clinical trials and any use of clinical services will require project review and approval by the Office of Research Agreements Management (ORAM) to assure availability of those clinical resources. Prior discussion with the appropriate clinical service chief is strongly encouraged)

Check all that apply

- [ ] Pharmacy
- [x] Laboratory
- [ ] Cardiology
- [ ] Radiology
- [ ] Nursing
- [ ] Nuclear Medicine
- [ ] MAS (Charts)
- [ ] Other (list below)

List others here

Section 27 - Protocol Attachments

If there is any material, such as tables or figures, that are referenced in the protocol text above but not pasted into the protocol application these can be attached in the Submission form along with other documents such as Consents and HIPAA Authorizations. press Save and Continue

Section 28 - Protocol Association to New or Existing Project

28) Is this a new R&D Project?. Before you go on to complete the *Initial Review Submission Form* (which is used for attachments), please address the association of this Protocol to an R&D Committee Project. This Protocol may represent a new R&D Project, or it may be an additional Protocol under an existing R&D Project (such as when a single grant supports multiple Protocols). Will this Protocol be submitted to the R&D Committee as a new Project?

- ○ Yes
- ◉ No

Section 29 - Existing Project Association

29) The associated R&D Project should already exist in the database. Identify the R&D Project(s) that correspond to this protocol.

Project Status	Proposal Number	Project Title	Principal Investigator
No Projects are Linked to this Study			

The Protocol Application is now complete for a Protocol attached to an existing Project.

Next you will go on to the Initial Review Submission Form. This form is used to collect the Application and any other needed attachments for submission to the IRB for review.

Press *Save and Continue*