STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: A Controlled Trial of Topiramate Treatment for Alcohol Dependence in Veterans with PTSD

NCT number: NCT01749215

Document date: 05/07/2018

A CONTROLLED TRIAL OF TOPIRAMATE TREATMENT FOR ALCOHOL DEPENDENCE IN VETERANS WITH PTSD

Principal Investigator:
Steven L. Batki, M.D.
San Francisco VA Medical Center
University of California, San Francisco
4150 Clement Street (116-E)
San Francisco, CA 94121
415/221-4810 x 3671
415/750-2187
steven.batki@ucsf.edu

Coinvestigators:
Thomas C. Neylan, MD
David Pennington, PhD

University of California, San Francisco
San Francisco VA Medical Center

PROPOSAL NUMBER: PT110423
PHASE IV
VERSION 11/5-7-18

TABLE OF CONTENTS

- D.3.k.6.f) Beck Anxiety Inventory (BAI)
- D.3.k.6.g) Suicide Risk Assessment
- D.3.k.6.h) Profile of Mood States (POMS)
- D.3.k.6.i) Pittsburgh Sleep Quality Index (PSQI)
- D.3.k.6.j) Insomnia Severity Index (ISI)
- D.3.k.6.k) Difficulties in Emotion Regulation Scale (DERS)
- D.3.k.6.l) Distress Tolerance Scale (DTS)
- D.3.k.6.m) Alcohol Purchase Task (APT)
- D.3.k.7) Neuropsychological Assessment
  - D.3.k.7.a) Decision-Making
    - D.3.k.7.a.i) Iowa Gambling Task (IGT)
    - D.3.k.7.a.ii) Delay Discounting (DD)
  - D.3.k.7.b) Risk-Taking
    - D.3.k.7.b.iii) Balloon Analogue Risk Test (BART)
  - D.3.k.7.c) Measures of Cognitive Functioning
    - D.3.k.7.c.iv) WAIS-III Digit Span
    - D.3.k.7.c.v) WAIS-III Arithmetic
    - D.3.k.7.c.vi) Controlled Oral Word Association (COWA)
    - D.3.k.7.c.vii) Hopkins Verbal Learning Task, Revised (HVLT-R)
    - D.3.k.7.c.viii) Trail Making Test (TMT) Parts A & B
    - D.3.k.7.c.ix) Wechsler Test of Adult Reading (WTAR)
  - D.3.k.7.d) Impulsivity
    - D.3.k.7.d.x) Stroop Inhibition
    - D.3.k.7.d.xi) Barratt Impulsiveness Scale II (BIS-II)
    - D.3.k.7.d.xii) Stop Signal Task
- D.3.k.8) Genetic Testing
- D.3.k.9) TBI Measures
  - D.3.k.9.a) Neurobehavioral Symptom Inventory (NSI)
  - D.3.k.9.b) Level 2 TBI Evaluation

D.3.l. Weekly Visit Schedule

- D.3.l.1) Screening Phase: Prescreening, Consent, Screening and Baseline Assessments
  - D.3.l.1.a) Prescreening
  - D.3.l.1.b) Informed Consent
  - D.3.l.1.c) Measures
  - D.3.l.1.d) Procedures
- D.3.l.2) Treatment Phase
  - D.3.l.2.a) Weeks 1, 2, 3, 5, 7, 9, 10, 11
  - D.3.l.2.b) Weeks 4, 8
  - D.3.l.2.c) Weeks 6, 12
- D.3.l.3) Follow-up Phase

D.4. Statistical Data Analysis

- D.4.a. Primary Outcome Measure
  - D.4.a.1) Primary Hypothesis
  - D.4.a.2) Data Analytic Technique for the Primary Outcome
  - D.4.a.3) Power Analyses for the Primary Outcome
- D.4.b. Secondary Outcome Measure
  - D.4.b.1) Secondary Hypotheses
  - D.4.b.2) Data Analytic Technique for the Secondary Outcome
- D.4.c. Exploratory Outcomes/Exploratory Hypotheses

- D.4.c.1) Exploratory hypotheses
- D.5. Data Sharing Plan
- D.6. Study Limitations/Potential Problems
- D.7. Time Sequence

E. Human Subjects Research Concerns
- E.1. Protection of Human Subjects
  - E.1.a. Risks to Subjects
    - E.1.a.1) Description of Human Subjects Involvement
    - E.1.a.2) Study Site
    - E.1.a.3) Characteristics of Study Population
    - E.1.a.4) Inclusion/Exclusion Criteria
    - E.1.a.5) Sources of Materials
    - E.1.a.6) Potential Risks
      - E.1.a.6.a) Risks of Topiramate
        - E.1.a.6.a)(1) The most common adverse events
          - E.1.a.6.a)(1)(a) In the clinical trial of topiramate monotherapy for epilepsy
          - E.1.a.6.a)(1)(b) In the multicenter trial of topiramate in alcohol dependence
        - E.1.a.6.a)(2) Adverse Events (AEs) leading to discontinuation
          - E.1.a.6.a)(2)(a) In the clinical trial of topiramate monotherapy for epilepsy
          - E.1.a.6.a)(2)(b) In the multicenter trial of topiramate in alcohol
        - E.1.a.6.a)(3) FDA warnings appear in Package Insert (U.S. Food and Drug Administration 2009)
          - E.1.a.6.a)(3)(a) Suicidality associated with anticonvulsants
          - E.1.a.6.a)(3)(b) Metabolic Acidosis
          - E.1.a.6.a)(3)(c) Acute Myopia and Secondary Angle Closure Glaucoma
          - E.1.a.6.a)(3)(d) Oligohidrosis and Hyperthermia
          - E.1.a.6.a)(3)(e) Withdrawal of AEDs
          - E.1.a.6.a)(3)(f) Cognitive/Neuropsychiatric Adverse Events
          - E.1.a.6.a)(3)(g) Kidney Stones
          - E.1.a.6.a)(3)(h) Other Rare Adverse Effects
          - E.1.a.6.a)(3)(i) Contraindicated Medications
      - E.1.a.6.b) Blood Drawing (Venipuncture) Risks
      - E.1.a.6.c) Reproductive/Pregnancy Risks
      - E.1.a.6.d) Risk to Privacy/Confidentiality
      - E.1.a.6.e) Effects of Topiramate on Other Medications
      - E.1.a.6.f) Randomization Risks
      - E.1.a.6.g) Risk of Relapse to Alcohol Use
      - E.1.a.6.h) Risk of Cessation of Current Alcohol Abuse Medication
      - E.1.a.6.i) Unknown Risks
  - E.1.b. Adequacy of Protection Against Risks
    - E.1.b.1) Informed Consent
    - E.1.b.2) Protection Against Risks
      - E.1.b.2)a) Risks of Topiramate
        - E.1.b.2)a)(1) Suicidality Associated with Anticonvulsants
        - E.1.b.2)a)(2) Metabolic Acidosis
        - E.1.b.2)a)(3) Acute Myopia and Secondary Angle Closure Glaucoma
        - E.1.b.2)a)(4) Oligohidrosis & Hypothermia
        - E.1.b.2)a)(5) Withdrawal of Anticonvulsants
        - E.1.b.2)a)(6) Cognitive/Neuropsychiatric Adverse Events
        - E.1.b.2)a)(7) Kidney Stones

I. SYNOPSIS

Alcohol use disorders (AUDs) and PTSD commonly co-occur, complicate assessment and treatment, and worsen clinical outcomes in veterans with both conditions. AUDs are potential consequences of PTSD, as many veterans may use alcohol in an attempt to "self-medicate" or ameliorate PTSD symptoms such as hyperarousal or emotional numbing. AUDs may also be a risk factor for the development of PTSD and may exacerbate PTSD symptom severity and impairment. Treatment for co-occurring PTSD and alcohol dependence among veterans is challenging. To date there has been little research to develop pharmacotherapies that would, ideally, reduce both alcohol use and PTSD symptom severity in patients with both of these conditions. Topiramate is one of the few medications for alcohol dependence that has also been separately tested as a potential medication to treat PTSD. Topiramate's efficacy in alcohol dependence in patients without PTSD has been shown in two recent large controlled trials. Open trials have suggested that topiramate may be effective in reducing PTSD symptoms in patients without AUDs, and a number of small controlled trials have also produced promising results. The PI recently completed the first pilot clinical trial of topiramate treatment in veterans with both alcohol dependence and PTSD, and preliminary analyses demonstrate feasibility, safety, tolerability, and efficacy in reducing alcohol use. Results also provide support for testing topiramate's potential efficacy in reducing PTSD symptoms.

This project consists of a controlled clinical trial of topiramate treatment to reduce alcohol use and PTSD symptoms in veterans with these co-occurring disorders. The specific aims are to: 1) definitively test the efficacy of topiramate in reducing alcohol use in veterans with PTSD and alcohol dependence; 2) test the efficacy of topiramate to reduce PTSD symptoms; and 3) explore if measures of impulsivity and decision-making predict treatment response and improve with topiramate therapy. To achieve these aims, we are conducting a prospective randomized double-blind controlled parallel-groups clinical trial of topiramate or placebo up to 300 mg per day, combined with weekly alcohol counseling, over a 12-week treatment period with a week 16 follow-up. The study population will consist of 150 male and female veterans between the ages of 18-69 who have concurrent diagnoses of alcohol dependence and PTSD. Subjects will meet with research staff weekly to receive study medication, manualized alcohol counseling, and research assessments. The primary treatment outcome will be the percent of days of drinking; the secondary outcome will be PTSD symptom severity. Exploratory measures will include assessments of impulsivity and decision-making.

This study is being sponsored by the Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC).

II. RESEARCH PLAN

A. GOALS AND SPECIFIC AIMS

The overall objective of the proposed project is to improve the care of veterans with alcohol dependence and co-occurring PTSD. The investigators will conduct a controlled clinical trial to test the efficacy of topiramate treatment in reducing alcohol use in patients with PTSD.

Alcohol use disorders (AUDs) and PTSD commonly co-occur, complicate assessment and treatment, and worsen clinical outcomes in veterans with both conditions. AUDs are potential consequences of PTSD, as many veterans may use alcohol in an attempt to "self-medicate" or ameliorate PTSD symptoms such as hyperarousal or emotional numbing. AUDs may also be a risk factor for the development of PTSD and may exacerbate PTSD symptom severity and impairment. Treatment for co-occurring PTSD and alcohol dependence among veterans is challenging. To date there has been little research to develop pharmacotherapies that would, ideally, reduce both alcohol use and PTSD symptom severity in patients with both of these conditions. Topiramate is one of the few medications for alcohol dependence that has also been separately tested as a potential medication to treat PTSD. Topiramate's efficacy in alcohol dependence in patients without PTSD has been shown in two recent large controlled trials. Open trials have suggested that topiramate may be effective in reducing PTSD symptoms in patients without AUDs, and a number of small controlled trials have also produced promising results. The PI is completing the first pilot clinical trial of topiramate treatment in veterans with <u>both</u> alcohol dependence and PTSD, and preliminary analyses demonstrate feasibility, safety, tolerability, and possible efficacy in reducing alcohol use as well as PTSD symptoms.

This project consists of a controlled clinical trial of topiramate treatment to reduce alcohol use and PTSD symptoms in veterans with these co-occurring disorders. The specific aims are to: 1) definitively test the efficacy of topiramate in reducing alcohol use in veterans with PTSD and alcohol dependence; 2) test the efficacy of topiramate to reduce PTSD symptoms; and 3) explore if measures of impulsivity and decision-making predict treatment response and improve with topiramate therapy. To achieve these aims, we are conducting a prospective randomized double-blind controlled parallel-groups clinical trial of topiramate or placebo up to 300 mg per day, combined with weekly alcohol counseling, over a 12-week treatment period with a week 16 follow-up. The study population will consist of 150 male and female veterans between the ages of 18-69 who have concurrent diagnoses of alcohol dependence and PTSD. Subjects will meet with research staff weekly to receive study medication, manualized alcohol counseling, and research assessments. The primary treatment outcome will be the percent of days of heavy drinking; the secondary outcome will be PTSD symptom severity. Exploratory measures will include assessments of impulsivity and decision-making.

A.1. PRIMARY AIM: To determine if topiramate treatment reduces alcohol use in veterans with PTSD

1.a. The primary aim is to definitively test the efficacy of topiramate in reducing alcohol use in veterans with PTSD and alcohol dependence.
1.b. The primary outcome will be the percent of heavy drinking days over the course of the study as measured by the Timeline Followback.
1.c. The primary hypothesis is that topiramate treatment will be more efficacious than placebo in reducing the proportion of heavy drinking days.

This hypothesis will be tested through a mixed-model statistical analysis of the between-groups differences in the proportion of heavy drinking days over the course of the clinical trial.

A.2. SECONDARY AIMS: To determine if topiramate reduces PTSD symptoms and alcohol use (using other alcohol use measures) in these patients.

The *secondary aims* are*:*
(2.1.a) To determine whether topiramate will be associated with a significant reduction in PTSD symptoms from baseline to the end of the trial, as measured by the PTSD Checklist (PCL); and to determine whether

topiramate will be more efficacious than placebo.
(2.2.a) To determine whether topiramate treatment will be associated with significant reductions in other alcohol

use measures (drinking days/week, drinks per drinking day, alcohol craving, and urine Ethyl Glucuronide [EtG]) from baseline to end of treatment; and to determine whether topiramate will be more efficacious than placebo

The *secondary hypotheses* are:
(2.1.b) Topiramate treatment -- combined with Medical Management alcohol counseling and added to ongoing TBI treatment as usual --will be associated with a significant reduction in PTSD symptoms from baseline to the end of the trial, as measured by the PTSD Checklist (PCL) from baseline to end of treatment; and there will be a significant effect of the treatment group, with the topiramate treatment group showing a greater reduction in PCL scores compared to placebo controls.
(2.2.b) Topiramate treatment -- combined with Medical Management alcohol counseling and added to ongoing PTSD treatment as usual --will be associated with a significant reduction in scores of other alcohol use measures from baseline to end of treatment; and there will be a significant effect of the treatment group, with the topiramate treatment group showing a greater reduction in scores on various alcohol use measures compared to placebo controls.

These hypotheses will be tested:
(2.1.c) Through a mixed-model statistical analysis of the within-topiramate group and between-groups differences in PCL scores over the course of the clinical trial.
(2.2.c) Through a mixed-model statistical analysis of the within-topiramate group and between-groups analysis differences in scores on alcohol use measures (drinking days/week, drinks per drinking day, alcohol craving and urine Ethyl Glucuronide [EtG]) over the course of the clinical trial.

A.3. EXPLORATORY AIMS:

The exploratory aims are:
(3.1) Measure impulsivity, decision-making, and risk-taking at baseline to assess the relationship between these domains and:
- alcohol use at baseline
- alcohol use over the course of the study

(3.2) Assess the relationship between *changes* in alcohol use over the course of the study and *changes* in:
- impulsivity
- risk-taking
- decision-making

(3.3) Assess the effects of topiramate versus placebo treatment on:
- impulsivity
- risk-taking
- verbal fluency, verbal memory

The exploratory hypotheses are:
(3.1) High impulsivity, high risk-taking, and poor decision-making at baseline will be associated with higher levels of alcohol use at baseline and over the course of the study;
(3.2) Reductions in alcohol use will be associated with reductions in impulsivity and risk taking, and improvement in decision-making;
(3.3) Topiramate will be associated with greater reductions in impulsivity and risk-taking, but also with greater impairment of verbal fluency and memory than placebo.

These hypotheses will be tested with mixed models similarly to the primary and secondary hypotheses.
(3.1) is assessed by the effect of baseline impulsivity and risk-taking (tested separately) on alcohol use over time.
(3.2) is tested by estimating subject-specific slopes from random coefficients mixed models predicting changes in alcohol use, impulsivity, and risk-taking, and calculating the Pearson correlation coefficients

between slopes of change in alcohol use and changes in impulsivity and risk-taking.
(3.3) is tested by the Group by Time interaction term in the mixed models predicting impulsivity, risk-taking, verbal fluency and verbal memory, from treatment group and time, with baseline values as covariates.

B. BACKGROUND AND SIGNIFICANCE

B.1 OVERVIEW: THE PROBLEM OF CO-OCCURRING ALCOHOL DEPENDENCE AND PTSD

Clinicians face difficult challenges in the treatment of veterans with co-occurring alcohol use disorders (AUDs) and chronic PTSD. Effective treatments are critically needed for the large number of patients with alcohol dependence and PTSD who may not be adequately managed with current therapies. This study directly builds on the PI's preliminary *controlled clinical trial of topiramate in veterans with PTSD and alcohol dependence (AD)*. It also follows work by other investigators that provides support for the hypothesis that topiramate may be effective in reducing alcohol use in patients who are still drinking heavily despite standard treatment for PTSD. Topiramate is one of the few medications with demonstrated efficacy treating alcohol dependence that may also possess efficacy in treating PTSD. The PI's preliminary data signaling possible efficacy in treating both of these co-occurring conditions provides strong support for conducting a definitive trial of topiramate treatment in veterans with alcohol dependence who also suffer from PTSD.

B.2 EPIDEMIOLOGY OF PTSD AND ALCOHOL USE DISORDERS: A CRITICAL PROBLEM

There is an urgent need to improve the treatment of veterans diagnosed with PTSD and co-occuring alcohol use disorders. PTSD and alcohol/substance use have high rates of co-occurrence in the general population -- the relative odds of substance use disorders (SUDs) in individuals with, versus without PTSD, ranges from approximately 2 to 8 in different studies[1]. Exposure to the stresses of combat is known to be associated with risk for both PTSD and for alcohol and other substance use. Combat-related PTSD is highly prevalent, chronic and often accompanied by substance abuse. Hoge and coworkers have reported an estimated 10-20% prevalence of PTSD in veterans who have served in Afghanistan and Iraq[2-3]. PTSD and alcohol use disorders also occur frequently among returning OEF/OIF veterans[4]. Between 23-31% of returning OEF/OIF National Guard troops with combat exposure suffered from PTSD or depression and half of these soldiers had coexisting problems with alcohol misuse and/or aggressive behavior[5].

Alcohol and substance use have a bidirectional relationship with PTSD. Alcohol and substance abuse are known risk factors for the development of PTSD, are moderators of PTSD symptom severity, and are also potential consequences of PTSD. AUDs and PTSD share some common neurobiological mechanisms, e.g. elevations in norepinephrine and glutamate[6-7]. AUDs are known risk factors for the development of PTSD, moderators of PTSD symptom severity, and potential consequences of PTSD. Alcohol is the most common substance of abuse in veterans with PTSD, and for some patients alcohol use may be an attempt to "self-medicate" or respond to symptoms such as insomnia, anxiety, and hyperarousal[8-9]. The co-occurrence of AUDs and PTSD is associated with worse psychosocial and medical outcomes, relapse to substance use, and rates of hospitalization[10]. However, heavy alcohol use may actually cause more severe psychosocial and medical problems. To date there have been only a few reported studies of pharmacotherapy for patients who have both of these co-occurring conditions[11-13] and no consensus is readily available regarding the optimal use of medications[10]. Advancing knowledge about the effectiveness of pharmacotherapies is necessary in order to improve the treatment of alcohol dependence in co-occurring PTSD.

B. 3 CURRENT MEDICATIONS FOR ALCOHOL DEPENDENCE: WHY THEY ARE INADEQUATE

Medications currently approved by the Food and Drug Administration (FDA) for the treatment of alcohol dependence are disulfiram, naltrexone in its oral and injectable forms, and acamprosate. These medications possess strengths but also have certain limitations. Disulfiram has been in use since the 1950s, although there have been few well-controlled studies on its effectiveness. One rigorous well-controlled double-blind study showed only questionable efficacy[14]. Disulfiram treatment requires commitment to abstinence from alcohol use because of the hazardous effects of the disulfiram-alcohol reaction. The possibility of liver toxicity early in treatment is the basis for a labeling recommendation that liver function tests (LFTs) be carried out before treatment with disulfiram is initiated, and again during treatment. Naltrexone, an opioid antagonist, was approved for the treatment alcohol dependence in the United States in 1994, based on two positive clinical trials[15-16]. Subsequent studies have generally supported the initial findings of reduced drinking and increased

length of abstinence, although not all clinical trials have shown positive effects. High-dose naltrexone has been associated with rare liver toxicity; therefore LFT monitoring is required and caution is advised in patients with hepatic dysfunction. Naltrexone's opioid antagonism poses a substantial disadvantage, precluding its use in patients who require opioid analgesic treatment, a highly salient limiting factor and barrier to its use in veterans who may have sustained painful injuries as a result of combat. Acamprosate, a structural analog of taurine, showed reduced relapse rates and craving for alcohol in European studies[17]. However, studies conducted in the United States, e.g. the COMBINE study[18] have not adequately established the efficacy of acamprosate. Because of the limitations of the currently available FDA-approved pharmacological agents, there has been a persistent need to identify alternative medications for the treatment of alcohol dependence.

B.4 PHARMACOTHERAPY FOR ALCOHOL DEPENDENCE IN PTSD: EARLY STAGES

Alcohol dependence (AD) medications, PTSD medications, and other agents have been or are being studied in the treatment of co-occuring AD and PTSD but only a few of these trials have been reported. Brady et al.[11-12] examined sertraline, finding it to have inconsistent effects on alcohol use; sertraline is under investigation by Hien as well[19]. Petrakis found naltrexone and disulfiram to have beneficial effects in a cohort of patients with co-occurring alcohol dependence and other psychiatric disorders including PTSD[13]. Naltrexone is also under investigation currently (Foa NCT 0004689)[20], as is prazosin (Petrakis NCT 00744055)[21] and a Substance P/Neurokinin-1 receptor antagonist (George NCT00896030)[22]. Anticonvulsants have also been investigated in the treatment of either alcohol dependence or anxiety/PTSD, but not for the co-occurrence of the two conditions. The anticonvulsants topiramate, gabapentin, pregabalin and others have been found to have some efficacy in treating alcohol dependence[23-26]. Anticonvulsants have also been proposed and tested in the treatment of anxiety disorders including PTSD[23]. The PI and coinvestigators have completed a pilot controlled clinical trial of the anticonvulsant topiramate in veterans with both conditions (Batki NCT01087736)[27].

B.5. NEUROBEHAVIORAL INTERACTIONS OF HEAVY ALCOHOL USE AND PTSD

Alcohol use disorders are associated with, or causal to, a wide variety of neurobehavioral harms that may also be related to PTSD. These include impulsivity, risk-taking behavior, irritability/mood instability, depression, suicide risk, as well as impairment in attention, concentration, visual-spatial memory, and executive functioning[12]. Both PTSD and alcohol use disorders independently may alter cognitive, emotional, and behavioral functioning. Both PTSD and alcohol are associated with cognitive impairment, shown to be an important moderator of substance abuse treatment outcome[13, 14]. Decision-making deficits are widely found in alcohol and other drug dependence[13-16]. Both PTSD and alcohol are associated with impulsivity and impaired decision-making, linked to ventromedial and orbitofrontal cortex dysfunction[13]. Neurocognitive impairment may therefore be an important contributor to, as well as a result of, alcohol use in PTSD. However, cognitive functioning has been shown to improve even after brief periods of abstinence from alcohol[13]. Reducing alcohol use may therefore have the potential to improve cognitive functioning and reduce risky behavior in veterans with PTSD.

B.6. IMPULSIVITY IN ALCOHOL USE DISORDERS AND PTSD

Alcohol dependence (AD) and PTSD are each associated with increased impulsivity with a potential for a synergistic increase in risk-taking as well as poor decision-making[17]. These cognitive impairments may be associated with high-risk behaviors. Little is known about the role of impulsivity as a possible predictor of, or a possible consequence of, heavy alcohol use in patients with PTSD. Moreover, there are no reports available regarding whether reductions in alcohol use may in turn reduce impulsivity in these patients. Pharmacobehavioral treatments could be further improved with a better understanding of the potential effects of medications in reducing impulsivity. Such an effect has recently been suggested by the work of Rubio and colleagues with topiramate[18] treatment of AUDs.

C. PRELIMINARY STUDIES

C.1. TOPIRAMATE TREATMENT OF ALCOHOL DEPENDENCE

C.1.a. Topiramate background:

Topiramate is an FDA-approved anticonvulsant and migraine treatment medication that has been shown to be significantly more efficacious in reducing alcohol use than placebo in two large double-blind controlled clinical trials[28-29] and several smaller studies. These studies demonstrated that topiramate significantly increased the

percent days abstinent from alcohol and reduced heavy drinking days and drinks per drinking day.

Topiramate is a sulfamate-substituted monosaccharide derived from fructose and is a structurally novel compound that is an effective anticonvulsant with a good safety profile after oral administration in animals and humans[30]. Topiramate has been approved for marketing in the United States for adjunctive treatment of patients with partial onset seizures, Lennox-Gastaut syndrome, or primary generalized tonic-clonic seizure, as well as for migraine prevention. Topiramate has multiple mechanisms of action that may contribute to its anticonvulsant properties as well as its potential therapeutic effects in the treatment of alcohol dependence. Topiramate inhibits voltage-gated sodium channels and suppresses action potentials associated with sustained repetitive cell firing[31], inhibits high voltage-activated (L-type) calcium channels[32], and facilitates neuronal potassium conductance[33]. Topiramate also augments the inhibitory chloride ion influx in neurons mediated by gamma.-aminobutyric acid (GABA)[34]. This effect is not blocked by flumazenil suggesting that the mechanism is different from that of benzodiazepines. Also, topiramate antagonizes the α-amino-3-hydroxy-5-methylisoxazole-4 propionic acid (AMPA)/kainate subtype of glutamate receptors[35]. It has no effect on the N-methyl-D-aspartate (NMDA) receptor subtype. It is also a weak inhibitor of type II and IV isozymes of carbonic anhydrase[36].

Topiramate was proposed for alcohol treatment because of its facilitation of γ-amino-butyric acid (GABA) function through a non- benzodiazepine site at the GABA-A receptor and the antagonism of glutamate activity at the AMPA and kainite receptors[29, 37]. Medications that modulate the effects of excitatory amino acids and/or facilitate GABA action in the midbrain have been shown to be associated with clinical effectiveness in the treatment of alcohol dependence[38-40]. It is hypothesized that medications which modulate excitatory amino acids can suppress conditioned cue responses to alcohol after short term abstinence[41], reduce the aversive effects of alcohol withdrawal related to increased glutamate and decreased central dopamine levels, particularly in the nucleus accumbens[42-43], and inhibit neuronal hyperexcitability[44] following alcohol withdrawal[45-46]. Of added relevance to alcohol treatment, topiramate is not hepatically metabolized. The major route of elimination is via the kidneys[47] and it is primarily eliminated unchanged in the urine.

C.1.b. Topiramate Treatment Trials in Alcohol Dependence:

There have been four large controlled trials of topiramate in the treatment of alcohol dependence in patients without PTSD. Johnson and coworkers[28] conducted the first double-blind randomized controlled 12-week clinical trial comparing oral topiramate and placebo for treatment of 150 individuals with alcohol dependence. Subjects were assigned to topiramate (escalating dose of 25-300 mg per day or placebo as an adjunct to weekly standardized medication compliance management. Primary efficacy variables were: self-reported drinking and plasma gamma-glutamyl transferase (GGT). The secondary efficacy variable was self-reported craving. At study end, participants on topiramate, compared with those on placebo, had 26.2% more days abstinent (p=0.0003), 3.1 fewer drinks per drinking day (p=0.0009), 27.6% fewer heavy drinking days (p=0.0003), and lower plasma GGT (p=0.0046). Topiramate-induced differences in craving were also significantly greater than those of placebo, of similar magnitude to self-reported drinking changes, and highly correlated with them. Topiramate (up to 300 mg per day) was judged to be more efficacious than placebo as an adjunct to standardized medication compliance management in treatment of alcohol dependence.

Johnson et al.[29] also carried out a second, larger, multi-center trial of topiramate in alcohol dependence – a double-blind, randomized, placebo-controlled, 14-week trial of 371 men and women aged 18 to 65 years diagnosed with alcohol dependence in which subjects received up to 300 mg/d of topiramate or placebo, along with a weekly compliance enhancement intervention. The primary efficacy variable was self-reported percentage of heavy drinking days. Secondary outcomes included other self-reported drinking measures (percentage of days abstinent and drinks per drinking day) along with GGT. Topiramate was more efficacious than placebo at reducing the percentage of heavy drinking days from baseline to week 14 (mean difference, 8.44%; p = .002). Pre-specified mixed-model analysis also showed that topiramate compared with placebo decreased the percentage of heavy drinking days (mean difference, 16.19%; p < .001) and all other drinking outcomes (p < .001 for all comparisons). Adverse events that were more common with topiramate vs. placebo, respectively, included paresthesia (50.8% vs. 10.6%), taste perversion (23.0% vs. 4.8%), anorexia (19.7% vs. 6.9%), and difficulty with concentration (14.8% vs. 3.2%).

Two other double-blind, randomized, controlled trials of topiramate have been conducted: Baltieri et al.[48] in a cohort of 155 alcohol-dependent patients, showed that topiramate was superior to placebo in increasing abstinence and reducing heavy drinking, and was possibly superior to naltrexone as well. Rubio et al.[49] found that topiramate was more efficacious in reducing heavy drinking in a sample of 63 alcohol-dependent subjects. Of particular interest in light of this application's exploratory aims, Rubio et al. also found that topiramate treatment was associated with improvement on measures of impulsivity including a continuous performance test and a stop-signal task, and that the improvement was associated with reduction in alcohol consumption[49]. In addition to these four placebo-controlled trials, several other open studies of topiramate have indicated effectiveness in alcohol dependence (reviewed by Johnson and Ait-Daoud[37]).

C.1.c. TOPIRAMATE IN PTSD TREATMENT

Topiramate has also been proposed as a treatment for PTSD, based on its pharmacological profile and its ability to inhibit kindling in animal models, in light of the potentially important role of kindling and sensitization of limbic nuclei in the etiology of PTSD[50]. In three open trials and four small-to-medium sized controlled trials, topiramate has shown some suggestions of at least partial effectiveness in reducing PTSD symptoms in patients without AUDs[51]. Open trials of topiramate by Berlant[50, 52] and Alderman et al.[53] yielded positive findings. The most recent of these was an 8-week open-label pilot study of topiramate for male combat veterans (N = 43) with PTSD, which also measured alcohol consumption[53]. In addition to reducing PTSD symptoms, the proportion of patients with high-risk drinking patterns (defined as >43 drinks/wk) also decreased (from 31% to 14%).

The four controlled trials in PTSD samples have had mostly positive results. Lindley et al.[54] in a controlled trial of 40 veterans, found that when used to augment standard PTSD pharmacotherapy, topiramate was associated with improving Clinician-Administered PTSD Scale (CAPS) re-experiencing symptoms more than placebo although it was also associated with more adverse effects and higher dropout. Tucker et al. also found that topiramate produced significantly greater reductions in CAPS re-experiencing symptoms than placebo in non-veterans with PTSD, although the difference in total CAPS scores was not statistically significant[55]. Davis (personal communication, 2008) reported the results of a third controlled trial of topiramate used as monotherapy in the treatment of PTSD, and found no overall CAPS improvement, although topiramate was associated with greater benefit in CAPS hyperarousal scores and clinical global improvement than placebo[56]. The fourth and most recent of the controlled trials, Yeh et al. studied a civilian sample and found that the topiramate experimental group demonstrated a significantly greater decrease in CAPS total score (topiramate -57.78; placebo -32.41; p=0.0076)[57]. Topiramate appeared to be effective in improving re-experiencing and avoidance/numbing symptom clusters in patients with PTSD.

C.2. PI's PILOT TRIAL OF TOPIRAMATE TREATMENT OF ALCOHOL DEPENDENCE IN VETERANS WITH PTSD

C.2.a. Overview:

The PI and co-investigators just completed (May 2012) an N=30, 12-week randomized, placebo-controlled pilot clinical trial of topiramate treatment of alcohol dependence in veterans with PTSD funded by the Department of Defense (Grant No. W81XWH-05-2-0094 to the Northern California Institute for Research and Education (NCIRE) Neuroscience Center of Excellence[27, 58]. This trial met pre-set primary and secondary outcome goals: the primary outcome goal was to determine if there was a significant within-group reduction of alcohol use in the topiramate treatment arm, from baseline to end of study. The secondary goal was to measure between-group differences and to determine if there was a signal of possible efficacy for topiramate over placebo, as indicated by a statistical trend (p<.10). This project has served to establish the feasibility of the PI's regulatory procedures, recruitment and retention strategies, Data Safety Monitoring Board and other safety monitoring approaches, medication dose, Medical Management counseling and web-based data entry system. The pilot study also used the measures proposed in this application, including the exploratory measures of impulsivity (Delay Discounting and BART), and the exploratory use of ethyl glucuronide as a biological measure of alcohol consumption. The research team has therefore had the opportunity to have worked out most of the problems encountered in clinical trials with alcohol-dependent PTSD patients and has had ample opportunity to design, de-bug, and fine-tune the methods that are to be utilized in the proposed study, substantially increasing the chances for its feasibility and successful completion. *[NOTE: This pilot*

study has been completed since our FY2011 Review and we report results on the full sample of 30 below.]

C.2.b. Analysis of Outcome of the Pilot Topiramate Trial:

We have conducted a preliminary analysis of outcome data from the 30 subjects who participated in the pilot topiramate trial. (NOTE: This pilot project was not designed to be adequately powered to determine significant between-group differences, but was *pre-hoc* designed to detect pre-post changes in the topiramate group and to have a reasonable chance of detecting a "signal" of differential efficacy, specified as a statistical trend ($p \leq .10$) toward improvement between groups.)

C.2.c. Baseline Characteristics:

Subjects had a mean age of 51.5 (25-65) years and 33.3% were non-White. They had high levels of alcohol use in the 90 days prior to screening with mean and median Percent Drinking Days of 77.7% and 85.6%, respectively, and also had severe PTSD symptoms (very high mean and median CAPS scores of 78 and 80, respectively) (see Table). Baseline characteristics of the Topiramate and Placebo groups showed no significant differences between the two groups on measures of alcohol use and PTSD symptom severity. Alcohol use and PTSD symptom severity were significantly correlated at baseline.

Table: Baseline Subject Characteristics (past 90 days)

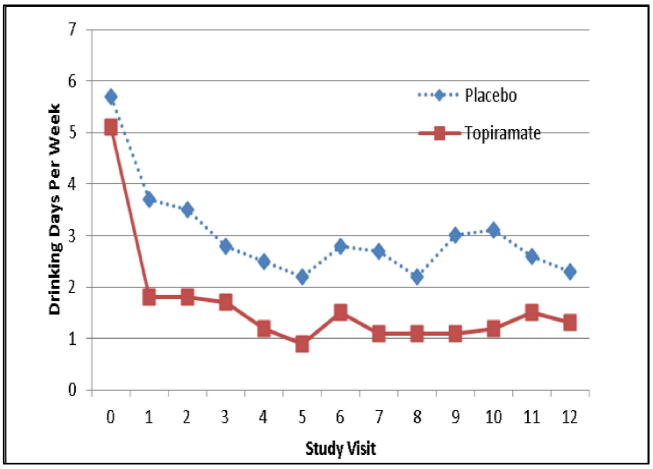
(All baseline *between-groups* differences were non-significant)	N=30 Total Sample		
	Mean	SD	**Median**
% Drinking Days (PDD)	**77.7%**	25.2	**85.6%**
% Heavy Drinking Days (PHDD)	**68.7%**	29.9	**77.8%**
Drinks per Drinking Day (D/DD)	**10.6**	5.7	**9.2**
Obsessive-Compulsive Drinking Scale (OCDS)	**103.2**	158.7	**47.5**
Clinical Assessment for PTSD (CAPS)	**78.2**	16.7	**80.5**
PTSD Checklist (PCL)	**57.8**	13.6	**59.5**

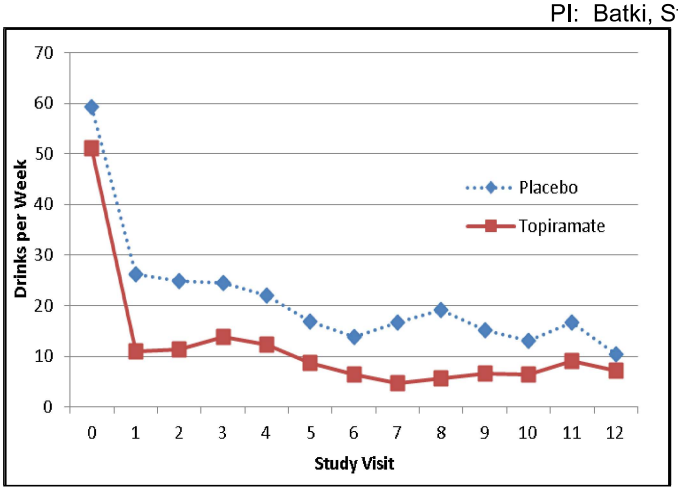
C.2.d. Outcomes: Alcohol use:

Topiramate was more efficacious than placebo in reducing the frequency of drinking days. A random intercept mixed effects Poisson model found that topiramate treatment resulted in significantly fewer Number of Drinking Days (NDD) per week over the entire 12 weeks of treatment, with baseline adjusted means of 1.37 (± 2.2) drinking days/per week in the topiramate and 2.8 (± 1.9) drinking days per week in the placebo group (**p=.037**) (means shown in Fig. 1). There was also a statistical trend toward significance for topiramate leading to fewer Number of Drinks per Week over the entire 12 weeks of treatment: 13.3 (±16.2) for topiramate vs. 21.8 (±23.2) for placebo (p = .095) (means shown in Fig. 2).

Figure 1: Significantly lower **Number of Drinking Days per Week** in Topiramate group controlled for baseline in mixed-model analysis (p=.032) (N=30; intent-to-treat analysis)

Figure 2: Trend toward lower **Number of Drinks per Week** in Topiramate group controlled for baseline in mixed-model analysis (p=.095) (N=30; intent-to-treat analysis)





C.2.e. Outcomes: Alcohol craving: Topiramate was more efficacious than placebo in reducing alcohol craving as measured by the Obsessive Compulsive Drinking Scale (OCDS). Alcohol craving scores were significantly lower in the topiramate as compared to the placebo group. Mean OCDS scores over the entire 12 weeks of the study were 7.6 (± 7.5) for the topiramate group and 15.4 (± 9.2) for placebo, (p=.004) (Fig. 3, below).

C.2.f. Outcomes: PTSD symptoms: PTSD Symptom Checklist (PCL) scores in the topiramate group were nonsignificantly lower than in the placebo group (Fig. 4, below). Mean baseline adjusted PCL scores over 12 weeks of treatment were 42.1 (±9.9) for Topiramate vs. 49.3 (±10.6) for placebo, p = .117.

Figure 3: Significantly (**p=.004**) lower **Alcohol Craving** in Topiramate group on the **Obsessive-Compulsive Drinking Scale (OCDS)** in mixed model analysis (N=30; intent-to-treat analysis)

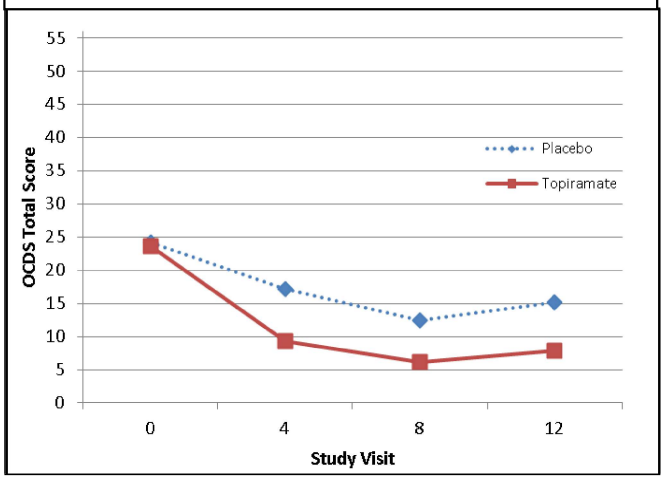
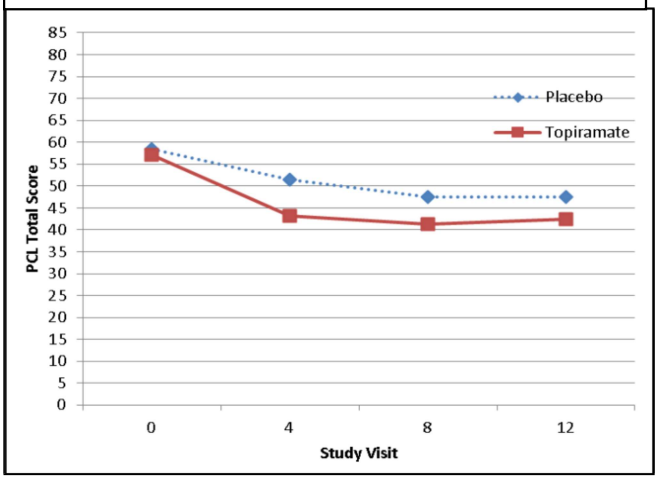


Figure 4: Nonsignificantly lower **PTSD Symptom Checklist (PCL)** (p=.117) scores in Topiramate group in mixed model analysis (N=30; intent-to-treat analysis)



C.2.g. Outcomes: Retention: Overall retention and attendance have been high. 83% have completed the study, attending an average of 88% of the weekly study visits. The topiramate group had significantly higher retention, mean11.5 wks attendance in the 12-week study vs 9.6 wks for placebo group (p<.05) (Fig. 5, below).

Figure 5: **Retention: Attendance** (%) at each weekly visit (N=30). The number of study visits attended was significantly higher in the Topiramate group (**p<.05**)

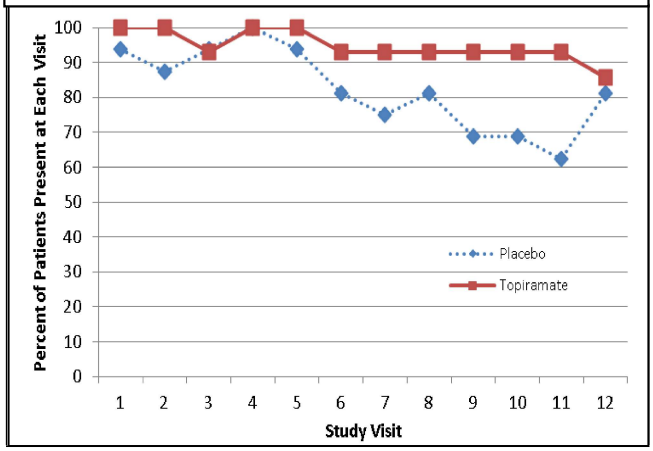
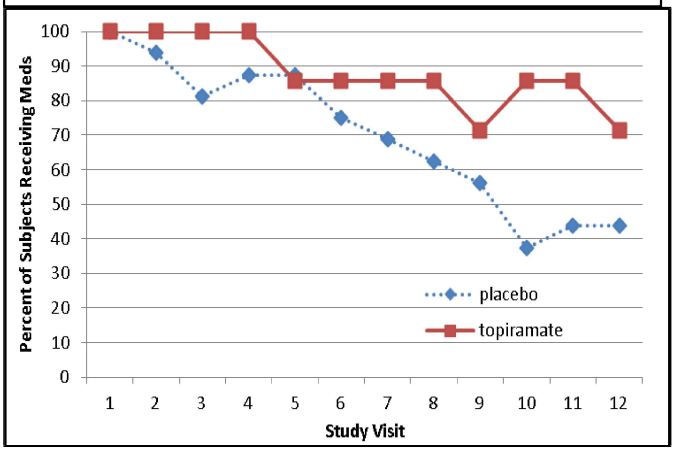


Figure 6: **Medication Adherence** (%) at each weekly visit (N=30). The number of study visits at which subjects took medication was significantly higher in the Topiramate group (**p<.05**)



C.2.h. Outcomes: Medication adherence and tolerability:

The topiramate group also had significantly higher proportion of medication adherence at each week (P<.05) (Fig. 6, above).There were no medication-related serious adverse events through the conduct of the entire trial, study medication has been well-tolerated, and retention has been higher in the topiramate group as compared to those assigned to placebo.

C.2.i. Conclusion:

The PI's preliminary work demonstrated the feasibility of recruiting, retaining, and treating patients with both AD and PTSD. The pilot provided extensive experience with the proposed dose of study medication, safety monitoring, and management of adverse effects. The trial met our *pre hoc* outcomes of showing significant reductions *within the topiramate group* in alcohol use and PTSD symptom severity from baseline to the 12 week treatment period. The pilot trial also met our secondary outcome goal of detecting a "signal" (a statistical trend or better) of efficacy for topiramate in reducing alcohol use and alcohol craving more than placebo, as reduction in days of drinking and in craving were significantly greater in the topiramate arm, and there was a statistical trend toward significance in reduction of the number of drinks per week, favoring topiramate. Results also showed a nonsignificant advantage in favor of topiramate being associated with greater reduction in PTSD symptoms. Moreover, study retention and medication adherence were significantly higher in the topiramate than in the placebo group. Because of these findings, we now propose the conduct of a larger, definitive controlled trial of topiramate treatment of alcohol dependence in patients with PTSD.

C.3. INNOVATION

1. Use of an anticonvulsant to target both alcohol use and PTSD symptoms: The proposed concurrent pharmacotherapy of both alcohol dependence and PTSD capitalizes on the dual potential efficacy of the anticonvulsant topiramate for treating both the PTSD symptoms and alcohol dependence. **2. Measures of impulsivity, risk-taking, and decision-making in a pharmacotherapy trial**: The proposed study also uses innovative exploratory measures including the use of serial measures of impulsivity, risk-taking, and decision making prior to start of medications and then over the course of the trial. We will explore the utility of these measures as predictors of outcome in the study. This may help to refine appropriate targeting of topiramate therapy. We will also look for changes in impulsivity, risk-taking, and decision-making as outcomes in response to topiramate treatment and alcohol use reduction. **3. Biological outcome measurement:** The innovative use of ethyl glucuronide as an exploratory alcohol use outcome will contribute to the state of knowledge regarding the utility of this measure in alcohol pharmacotherapy research.

D. RESEARCH DESIGN AND METHODS

D.1. GENERAL DESIGN

We propose a controlled clinical trial of topiramate treatment to reduce alcohol use and PTSD symptoms in

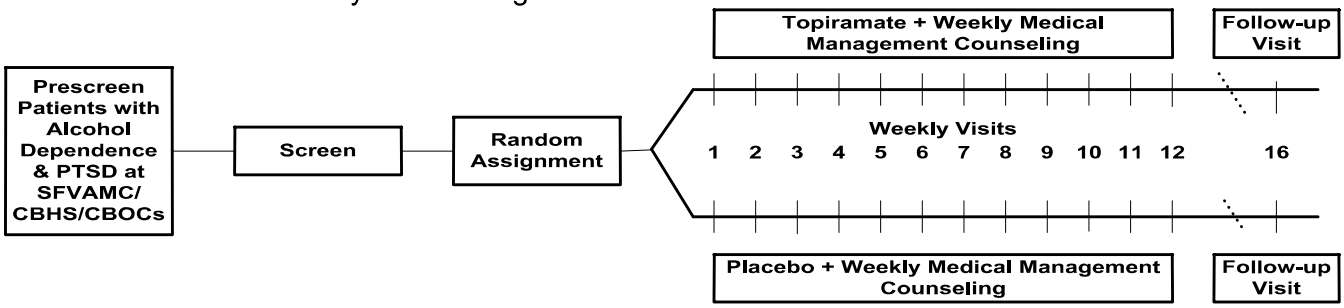
veterans with alcohol dependence and PTSD.

D.1.a. Rationale for a Controlled Trial of Topiramate:

We propose a more definitive controlled trial of topiramate treatment of alcohol dependence in veterans with PTSD. A placebo-controlled trial is justified because it is still the standard in the field, because there are no proven medications for concurrent AD and PTSD, and because very close weekly safety monitoring will occur (please see Human Subjects section). Moreover:

1) There are no reports to date, either positive or negative, of controlled trials testing the safety and efficacy of topiramate in patients with both PTSD and alcohol dependence, other than the PI's pilot study.
2) The PI's controlled pilot trial found significantly lower alcohol use in the topiramate vs placebo arm. However, the recently completed pilot study was not powered adequately to allow a definitive conclusion regarding topiramate's efficacy in the treatment of alcohol dependence and PTSD.
3) A controlled trial would also offer the opportunity to more definitively and accurately assess the incidence of treatment-emergent adverse events for topiramate as compared to placebo, and would provide a more accurate sense of the safety of topiramate in patients with both PTSD and alcohol dependence.

D.1.b. Overview of Design: To achieve these aims, we will conduct a prospective, parallel groups, randomized, double-blind, placebo-controlled flexible-dose clinical trial of topiramate in 150 male and female veterans with PTSD and alcohol dependence. The 16-week clinical trial will have as its primary treatment outcome the number of Days of Drinking alcohol.



The 12-week treatment phase consists of treatment with study medication (topiramate or placebo), plus weekly manualized alcohol counseling, added to whatever usual PTSD treatment subjects may be receiving, including medication (exceptions being any other alcohol treatment medications). [*NOTE: In response to the FY2011 Review of our previous submission, we specify that concomitant medications are recorded and coded as to specific medication as well as to class (e.g. antidepressant)and will be used for both descriptive and exploratory statistical analysis at study completion.*]

Topiramate or placebo treatment will begin with a 5-week titration period, continue with a 6-week maintenance period, and conclude with a 1-week taper period. Following the 12 weeks of treatment, there will be a follow-up visit in week 16.

Subjects will continue to receive usual care for PTSD and other medical and psychiatric disorders from their primary medical and mental health treatment providers. Subjects will meet with research staff weekly to receive medication, manualized counseling for alcohol use disorders, medication adherence feedback, and research assessments during the 12 weeks of medication treatment. Subjects will also be assessed at the week 16 follow-up visit. Additional visits may be conducted if needed to complete study measures. [*NOTE: In response to the Review of our FY2011 submission, we will not conduct interim telephone contacts by the research staff between visits.*]

Manualized counseling for alcohol use disorders will consist of Medical Management, an NIAAA manual-driven, low-intensity supportive program to foster, maintain, and promote adherence to the medication regimen and to promote continuation in the study[59].

D.2. STUDY PARTICIPANTS

a. Overview of Participants

Subjects will be recruited from the San Francisco VA Medical Center and will be men and women, ages 18 through 69, with a diagnosis of chronic PTSD plus current (past month) diagnosis of alcohol dependence. In addition, subjects must report current (past 30 day) "risky/hazardous" or "heavy" drinking by NIH/NIAAA criteria, on an average weekly basis, consisting of an average of 15 or more standard drinks per week for men and 8 or more standard drinks per week for women during the 30 days prior to Screening[59].

1) Recruitment

Veterans will be recruited from the Mental Health Service of the San Francisco VAMC and affiliated satellite clinics (Community-Based Outpatient Clinics [CBOCs] in Downtown San Francisco, Santa Rosa, CA, and San Bruno, CA), regional Vet Centers and mental health clinics.

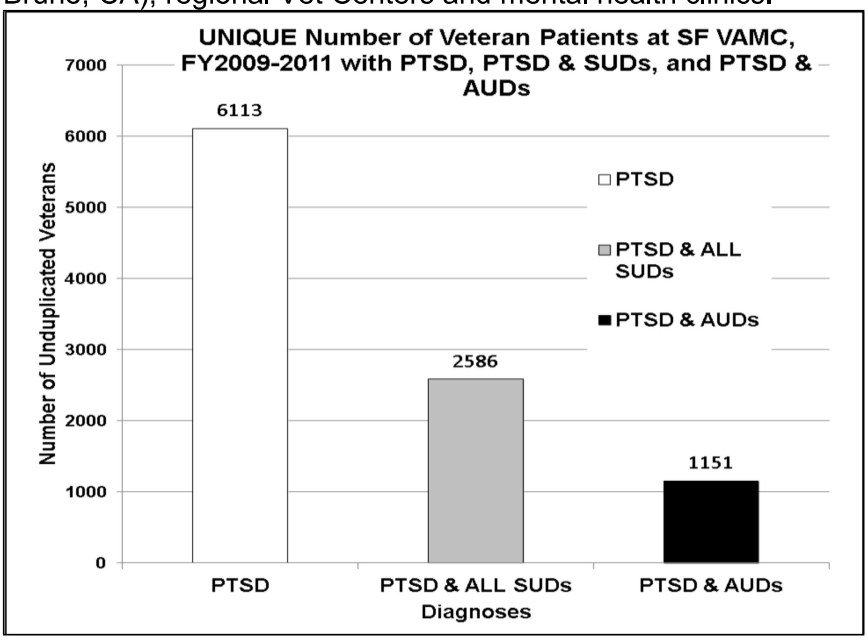


Figure 7: Total number of unique veteran patients at the San Francisco VA Medical Center, for the three year period FY2009 through 2011, indicating numbers of veterans with PTSD, veterans with PTSD plus any substance use disorders (SUDs), and veterans with PTSD plus alcohol use disorders (AUDs). The data indicates that there were 1,151 unduplicated veterans with both PTSD and alcohol use disorders documented in their medical record over the 3-year interval. This is probably an underestimate, since it is known that diagnoses for alcohol use disorders tend to be underrepresented in the medical record. Projecting from the 3-year data shown here, we therefore anticipate that over the 4-year study period more than 1,200 unduplicated veterans with PTSD and alcohol use disorder diagnoses will be available for potential recruitment for the target N=150 subjects.

Recruitment will be through direct outreach to patients via notices and cards in patient areas and asking clinicians to refer patients. Research staff will conduct brief pre-screening to assess possible eligibility. At the SFVAMC, sites will include the Primary Care, PTSD Clinic, Mental Health and Substance Abuse clinics, and affiliated satellite clinics (Community-Based Outpatient Clinics [CBOCs] in Downtown San Francisco, Santa Rosa, CA, and San Bruno, CA), regional Vet Centers and mental health clinics. The Investigator and Research Coordinator will work with staff in outpatient units at the SF VAMC and explain the study, including eligibility criteria, and publicize the study. Clinic how to refer a potential study candidate and how prospective subjects can contact study staff. Recruitment will be accomplished through: direct outreach to patients via posted notices and cards placed in patient areas, and asking clinicians to refer patients to the study. Once a prospective subject has been identified, research staff will conduct a brief telephone or in-person pre-screening interview to assess possible eligibility. If pre-screening is successful, research staff will obtain written informed consent and gather demographic and locator information including contact information for the patient's treatment providers. Written permission will be obtained for research staff to review mental health records and consult with the participant's primary care provider, psychiatrist, and other clinicians to obtain clinical information to assist in the assessments of medical, status, psychiatric diagnoses, and substance use. The PTSD or primary care, and mental health providers will also be asked for their assent to any patient entering the study to ensure it is medically and psychologically safe for a Veteran to participate in the research study.

C.1.c.2) Inclusion Criteria

1) Male and female veterans eligible for VA services.
2) Ages18 to 69 (inclusive).

3) Current DSM-IV diagnosis of PTSD.
4) Current (past month) DSM-IV diagnosis of Alcohol Dependence
5) Level of drinking must meet criteria for "at-risk " or "heavy" drinking by NIAAA threshold (NIAAA 2007): at least 15 standard drinks per week on average over the 4 weeks prior to study entry for men and at least 8 standard drinks per week on average for women. For Veterans who have been in a controlled drinking environment at study entry, eligibility criteria will be based on meeting "heavy" drinking criteria over the 4 weeks prior to entering the controlled drinking environment.
6) Subjects must express a desire to reduce alcohol consumption with the possible long-term goal of abstinence.
7) Female subjects must have a negative urine pregnancy test and must be either postmenopausal for at least one year, or practicing an effective method of birth control (e.g., surgically sterile, spermicide with barrier, male partner sterilization; or abstinent and agrees to continue abstinence or to use an acceptable method of contraception, as listed above, should sexual activity commence)
8) Subjects must have a Breath Alcohol Concentration (BAC) of 0.00% when signing informed consent.

C.1.c.3) Exclusion Criteria

1) Psychotic disorders, bipolar disorder, dementia, or other psychiatric disorders judged to be unstable.
2) Subjects known to have clinically significant unstable medical conditions, including but not limited to:
   -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 $\leq$ 60 mL/min
   -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
3) History of glaucoma.
4) History of nephrolithiasis.
5) Concurrent participation in another treatment study.
6) Female patients who are pregnant or lactating.
7) Current Topiramate use or use within the past 4 weeks.
8) Current medications for alcohol dependence (disulfiram, naltrexone, or acamprosate) or use in the past week.
9) Needing acute medical detoxification from alcohol based on a score of 12 or more on the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-AD).
10) Subjects who are legally mandated to participate in an alcohol treatment program.
11) Subjects who have had a suicide attempt in the past 6 months or suicidal ideation, with intent, in the 30 days prior to enrollment.
12) Subjects who have previously been treated with topiramate for any reason and discontinued treatment due to an adverse event or due to a hypersensitivity reaction to topiramate.
13) Subjects who in the opinion of the investigator should not be enrolled in the study because of the precautions, warnings or contraindications outlined in the topiramate package insert.

C.1.c.4) Naturalistic approach to inclusion of subjects

[*NOTE: In response to the Review of our FY2011 submission, we are clarifying that veterans will not be excluded for substance use disorders involving non-alcohol substances. The majority of veterans with PTSD and alcohol dependence use non-alcohol substances such as nicotine, cannabis, cocaine, opioids, etc. We will continue the same naturalistic approach as we have applied in our completed pilot controlled trial of topiramate --recruiting subjects who meet the above inclusion criteria and who do not have any of the above exclusion criteria, but allowing other forms of substance use disorders as long as alcohol is the primary substance of abuse (as indicated by alcohol being the main focus of clinical attention by clinical providers). We believe that selecting a subset of "pure" patients with only alcohol dependence and PTSD would create a study that may not be generalizable to the broader universe of patients with these co-occurring disorders. However, in response to concerns expressed in the review, we will balance the assignment of subjects with and without stimulant and opioid dependence to topiramate and placebo using an urn randomization procedure[111]*]

D.3. STUDY PROCEDURES

a. Overview of Study Procedures

The study will consist of three phases: a screening phase, a treatment phase, and a follow-up visit. During the treatment phase, double-blind randomized topiramate or placebo treatment will be provided for 12 weeks. Subjects will meet weekly with research staff at the San Francisco VA Medical Center. All subjects will receive Medical Management (MM), a manual-driven, low-intensity supportive program to foster, maintain and promote compliance with the medication regimen and to promote continuation in the study, on a weekly basis throughout the study. Adverse events will be assessed weekly over the 12 weeks of treatment.

b. Recruitment

All of the recruitment mechanisms described below have been worked out and applied in the PI's current pilot controlled study of topiramate treatment of alcohol dependence in veterans with PTSD (see Narrative section for description of the pilot study). Veterans will be recruited from the Mental Health Service of the San Francisco VAMC and affiliated satellite clinics, regional Vet Centers and mental health clinics, as well as from the Primary Care Medicine clinics. The Investigator and Research Coordinator will work with all staff in the PTSD Clinical Team, the Substance Abuse Program, and other outpatient units at the SF VAMC and its Community-Based Outpatient Clinics (CBOCs) as well as the SFVAMC's San Francisco City College (CCSF) Veterans Welcome Center. Research staff will explain the purpose and scope of the study, including eligibility criteria, to SF VAMC staff and will engage in a continuous process of publicizing the study. Hospital and clinics staff will be told whom to contact to refer a potential study candidate and how to have prospective subjects contact study staff.

Recruitment will be accomplished through a variety of mechanisms including: a) letters, calls, inservices, and other outreach programs aimed at clinical mental health and primary care providers; b) direct outreach to patients via posted notices and cards placed in patient areas; c) outreach to student veterans at City College of San Francisco; d) through online ads on websites like Craigslist or City College student veterans' website, and through public service announcements. Once a prospective subject has been identified, research staff will conduct a brief telephone or in-person pre-screening interview to assess possible eligibility. If pre-screening is successful, research staff will obtain written informed consent and gather demographic and locator information including contact information from the patient's treatment providers. Written permission will be obtained for research staff to review mental health records and consult with the participant's primary care provider, psychiatrist, and other clinicians to obtain clinical information to assist in the assessments of medical, status, psychiatric diagnoses, and substance use.

The primary care and mental health providers will also be asked for their assent to any patient entering the study.

Additionally, recruiters will access a pool of shared participants utilizing a password-protected database called Clinical Trial Management Software. Individuals in this database have been asked brief screening questions from a Program Wide Prescreen, which is described in depth in approved Protocol 12-09158, or from a specific study. Recruiters will contact individuals from this database who can decide if they want to answer the study specific screen. Informed consent will be obtained by research staff prior to beginning any procedures.

Finally, letters will be mailed to potential participants (as identified above) describing how the PI obtained their name and addresses and why these letters are being sent to them (**See Opt-Out Letter**). The letter will describe the research study and will invite veterans to call the lab manager. We will also provide an information sheet describing the details of the study so that potential participants are aware of why this research is being done and what participation entails. (**See Information Sheet**). A pre-addressed, stamped postcard will be included in the letter which a patient can return to indicate that they do not wish to be contacted for this study (**See Opt-Out Postcard**).

We will wait to contact potential participants for 2 weeks after the initial mailing to allow them time to opt-out if they do not wish to be contacted. If the team receives no returned "opt-out" postcard at least 14 days after the original mailing, we will attempt to contact the veteran by telephone, but will adhere to strict confidentiality. We will speak only to the patient once identified. If study staff were to reach a non-study participant, he/she would

state only that they are calling from the SFVAMC and will not disclose any information pertaining to the study. If a patient states that he/she does not wish to be in the study, we will respectfully not call again. If an opt-out letter is returned to the SFVAMC due to an incorrect mailing address, we will try to make contact via phone. If we are unable to reach a patient after 5 attempts, we will stop all efforts to make contact.

A new method of recruitment has been added to the list of ways we will try to connect with potential veteran-subjects. A brief, 3-question screener (**See Intake Screener**) asking about alcohol use, posttraumatic stress disorder (PTSD) diagnosis and the occurrence of a traumatic brain injury (TBI) will be passed out to veterans attending intake visits in the mental health and primary care clinics at the San Francisco VA Medical Center. Veterans will not be required to fill out the form if they are not interested in the study. If they are interested in the study, but do not want to fill out the screener, they may contact study staff directly via phone. If a veteran does complete the Intake Screener, he/she will be asked to place the screener in a sealed envelope and return to the front desk at the clinic. The screener-in-envelope will be placed in the VA inter-office mail folder and returned directly to study staff. Because the Intake Screener contains PHI (Last Name; Last 4 digits of social security number; and Phone Number) in addition to sensitive information concerning addiction, PTSD and TBI, we will follow the VA Directive 6609 and place the screener in an envelope labeled with **VA Directive 6609, Appendix B**, to ensure that special attention is given to the contents in the rare case that it is intercepted or lost. When study staff receives an Intake Screener, it will be stored separately from other data collected throughout the study, in a locked cabinet in a locked room.

c. Description of the Informed Consent Process

1) Prescreening

Due to the sensitive nature of the diagnoses we are studying (PTSD and substance use disorders) it is important to pre-screen for potential study eligibility before engaging patients in the lengthy and intrusive procedure of the full study informed consent and screening process. A waiver will be obtained from the IRB for this pre-screening process.

Prospective subjects will undergo a brief in-person or telephone pre-screen which will establish that they are: veterans, 18-69 years of age, receive treatment at the SFVAMC for PTSD, drink heavily by NIAAA criteria[59] and wish to reduce or stop alcohol use.

2) Consenting

After passing the prescreen process, and after the nature of the study has been fully explained, prospective subjects will be invited to give their written informed consent to enter the study.

The PI or an authorized member of the investigational staff will explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that their records may be accessed by competent authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions.

3) Breath Alcohol Test Prior to Consent

Prior to signing the consent, a breath alcohol test will be administered. If the breath alcohol test reading is greater than 0.00%, the subject will be asked to return later that day, or on another day, to be retested and to then provide written informed consent.

After this explanation and before entry to the study, consent will be appropriately recorded by means of the subject's dated signature. After having obtained the consent, a copy of the signed and dated informed consent form will be given to the subject.

The informed consent will be stored separately from other data collected throughout the study, in a locked

cabinet in a locked room. Informed consents will be stored indefinitely, and always in accordance with VHA's Record Control Schedule. A copy of the informed consent will also be scanned into each subject's CPRS record.

d. Screening

After obtaining informed consent, subjects will be listed on the Subject Screening Log and scheduled for screening assessments. The screening phase should be accomplished over a total of approximately 2-3 visits extending over approximately one week.

e. Random Assignment

[*NOTE: Per recommendations from the FY 2011 Review, we are adding detail to the description of the randomization procedure.*] Subjects will be stratified by gender, then randomized to receive either topiramate or placebo in a 1:1 ratio according to a computer-generated code provided by the study biostatistician. Urn randomization will be utilized for the following variables: abstinence from alcohol in the 4 days prior to randomization, commitment to abstinence versus alcohol use reduction as determined by response to the Thoughts About Abstinence questionnaire, and presence or absence of opioid or stimulant dependence (these variables have been selected as there is reason to believe that they may influence alcohol pharmacotherapy outcome). [*NOTE: Per recommendations from the FY 2011 Review, while we are retaining our intention to recruit veterans with PTSD and alcohol dependence even if they have concurrent non-primary opioid or stimulant dependence, we intend to control for these co-occurring disorders through the urn randomization procedure.*]

f. Pharmacotherapy

The pharmacotherapy phase will begin with random assignment followed by 12 weeks of treatment with topiramate or placebo. Subjects and investigators will be blinded to treatment assignment. Subjects will be randomized sequentially as they qualify for the study. To maintain the blind, sealed envelopes containing the study drug identification (e.g. topiramate or placebo) will be kept together, in a limited access area (the study biostatistician's office) that will be available to the investigators should the blind need to be broken for any individual subject. The study medications will be identical in appearance and will be packaged in identical containers. Subjects will be provided with 10 days of medication at each weekly visit to increase the likelihood of medication continuity in case of a missed visit. Extra medication will be collected from subjects at each visit.

Study medication (topiramate or placebo) will be titrated up over 5 weeks. Study medication will be started at a dose of 25 mg per day, given in the evening, and then increased in the second week, as tolerated, to 25 mg twice per day; in the third week to 50 mg twice/day; in the fourth week to 75 mg twice/day; in the 5th week to 100 mg twice/day; and in weeks 6-11 increased to and maintained at 100 mg in the morning and 200 mg at night, closely approximating the method of Johnson et al.[29] and identical to the PI's current pilot study (Batki NCT 01087736)[27]. Patients will be treated with the highest dose tolerated, not to exceed a total of 300 mg per day. The titration rate may be adjusted as needed. Dose adjustments are permitted throughout the titration period. Once the dosage at the end of the titration period is reached, subjects will be encouraged to maintain this dosage for the remainder of the treatment phase. Upon completion of the 6 week maintenance period subjects will taper off medication over a 7-day period (Week 12). All dosing will occur in a twice-daily regimen except for the first week of the study, which will be a single evening dose of 25 mg. If the subject experiences significant side effects during the titration period, the dosage may be adjusted as necessary.

The drug manufacturer has no involvement with the study. The Drug Product Services Laboratory (DPSL) at the University of California, San Francisco will purchase and supply our lab with USP or NF grade topiramate study capsules and matching placebo capsules. The policies and procedures of DPSL concerning good compounding practices and environmental, instrumental, and procedural quality assurance have been approved by the California State Board of Pharmacy. The SFVAMC Research Pharmacist will directly receive all study drug from DPSL and store in a limited access area or in a locked cabinet under appropriate environmental conditions. A participant must be present at the study visit to receive a 10 day supply of study medication/placebo. The dosage is to be determined by a study physician at each weekly visit, using the titration schedule as a guide. An official VA prescription form must be filled out by a study physician for each

patient at each visit. A research associate will drop off the prescription and pick up the medication/placebo from the SFVAMC pharmacy. Before dispensing the medication/placebo, the research associate will document the date, time and amount of study drug dispensed. This information will also be recorded in the subject's electronic medical file. Subjects are instructed to return all unused study medication. The number of returned capsules will be documented.

g. Medical Management Counseling for Alcohol Use Disorders and Other Procedures

We have selected a manualized, 12-session version of the NIAAA Project COMBINE study alcohol counseling, "Medical Management" (MM)[25]. This intervention has been designed to increase problem recognition, enhance motivation to change maladaptive patterns of alcohol use, and facilitate engagement in alcohol treatment (such as pharmacotherapy and AA). Participants will receive weekly Medical Management sessions for a total of 180-360 minutes consisting of 12 weekly individual sessions lasting 15 to 30 minutes each. The goal of MM is to help patients maintain adherence with the medication regimen using strategies that can be delivered by a typical health care provider. MM approximates a primary care approach to alcohol dependence and supports the use of pharmacotherapy. During the initial visit, the clinician reviews the patient's assessments, highlighting symptoms of alcohol dependence and the need for treatment. The patient is advised to stop drinking, educated about unhealthy alcohol use, provided a rationale for medication, and instructed on the importance of daily medication adherence. The clinician and patient also jointly develop an individualized medication-adherence plan; the patient is encouraged to attend support groups and is given information on the medications. At follow-up visits, drinking behavior and medication adherence are ascertained, and plans for reducing drinking or achieving abstinence are revised as needed. In each session, the MM administrator will communicate and discuss medication effects, subjects' concerns about any side effects and compliance barriers with the subject in understandable terms.

[*NOTE: In response to the Review of our FY 2011 submission, variability in delivery of the Medical management counseling will be minimized in the following ways.*]
Training will be provided to the research MD, RN and psychologist who will be MM administrators. The PI and his appointees will monitor MM sessions via audiotapes and provide training and guidance to the MM administrators as needed.

h. Medical Event Monitoring System (MEMS)

In order to monitor medication adherence and provide feedback about adherence to subjects, the study will use Medication Event Monitors (MEMS®) caps that attach to standard medication bottles. The MEMS cap contains a microprocessor that records the date and time of every bottle opening. Patients will be asked to bring the medication bottle with the MEMS cap to all scheduled visits for refills and a feedback session. Data are downloaded onto a PC with proprietary software. Use of microelectronic monitoring data to provide feedback to patients has been shown to improve compliance[67]. In addition, we plan to use the calendar plots generated for compliance feedback to help patients recall their substance use during the timeline follow-back assessments.

i. Phlebotomy and Urine Drug Testing

Phlebotomy will be performed at screening, week 6 and 12. Urine drug screens will be performed at week 4, 8, 12, and 16. Urine will be collected for EtG tests at each visit.

j. Participant Payment

Participants will be compensated in cash, check or debit card for their time, effort and travel costs after each completed visit. The screening visits at baseline will be reimbursed based on the completion of tasks. The payment schedule for baseline/screening measures and procedures is listed below. Participants will receive $20 for completed visits on Weeks 1, 2, 3, 5, 7, 9, 10, and 11. The longer visits of Weeks 4 and 8 will be compensated at a rate of $30. The longest visits, those of Weeks 6, 12, and 16, will be paid at a rate of $35 for each completed visit. Subjects will also be compensated $5 at each study visit during weeks 1-12 for returning study medication bottles. Details regarding compensation are outlined below and in the informed consent form. Participants can therefore earn up to a total of $530 for the full 16-week study participation.

If a subject lives outside of the San Francisco city limits and it takes over an hour to get to the SFVAMC, then

the subject will recieve $0.51 per mile (NCIRE travel reimbursement policy). MIleage will be calculated using the Google maps "DIRECTIONS" function, using the subject's home address as the starting point and the SFVAMC address as the point of destination.

PAYMENT SCHEDULE FOR BASELINE/SCREENING MEASURES/PROCEDURES

MEASURES/PROCEDURES	AMOUNT
Informed Consent	---
TLFB/Patient Locator	$10
SCID	$5
CAPS	$10
TBI Evaluation	$10
CTSI	$10
Self-report measures – (21 total)	$10
Neurocog	$20
Med Mgmt	$5
AEs/ConcomMeds/Concom Txt	$5
TOTAL AMOUNT	$85

WEEKLY COMPENSATION SCHEDULE

VISIT	STUDY VISIT	+ MEMS CAP	TOTAL
SCREENING	$85	---	$85
WEEK 1	$20	$5	$25
WEEK 2	$20	$5	$25
WEEK 3	$20	$5	$25
WEEK 4	$30	$5	$35
WEEK 5	$20	$5	$25
WEEK 6	$35	$5	$40
WEEK 7	$20	$5	$25
WEEK 8	$30	$5	$35
WEEK 9	$20	$5	$25
WEEK 10	$20	$5	$25
WEEK 11	$20	$5	$25
WEEK 12	$35	$5	$40
WEEK 16	$35	---	$35
TOTAL			$470

k. Measures and Schedule of Data Collection

1) Overview (See Table 1 for Schedule of Measures)

The screening phase will typically be 1-2 weeks in duration, with approximately 3 screening appointments conducted. Following screening, study participation will last 16 weeks, consisting of a 12-week topiramate or placebo treatment phase with weekly counseling and research visits followed by one follow-up research visit at week 16.

Efforts will be made toward reducing the amount of missing data by: (a) use of a collateral informant to assist in locating patients; (b) telephone follow-up to make contact with missing patients; (c) establishment of flexible, but acceptable, time periods for the completion of each assessment; and (d) some self-report and interview measures may be administered by telephone to collect missing data from patients unwilling or unable to visit research sites to participate in a scheduled assessment session.

Establishment of flexible, but acceptable time frames for completion of research assessments:
All research assessments should be completed within an established window. Assessments scheduled for weeks 1, 2,3,5,7,9,10, and 11 will have a window of ±3 days for completion. Assessments scheduled for weeks 4, 6, 8, 12, and 16, have a window of ±1 week for completion. This flexibility will enhance the ability of staff to schedule patients for assessments as close as possible to the protocol defined period. Patients likely

to miss appointments should be scheduled early in the window to allow for successive attempts to complete ratings within the desired time frame.

After receiving CHR and R&D approval, we will be converting most of our questionnaire measures to a digital format, so that this questionnaire data can be collected and managed using the San Francisco VA Medical Center's Stress and Health Research Program Data Management Research Database System.

The Research Database System will include FDA regulated and non-regulated research studies. The SQL Server Database Engine is the core service for storing, processing, and securing data within the enterprise. Clinical study databases built in sql server also have a data change tracking mechanism, (i.e. audit trail) identifying data changes made by who, when, what changed, and reason for change.

Electronic data transfer is serviced from a number of external computer applications where data points are generated and stored based on a subject interfacing with a computer application. Implementation of process flow allows the transfer of data between the sql server database and a wide variety of data formats. Additional safeguards include using user authentication to access data on the research server. Different user profiles allow access to specific tables of the sql server database. For example, investigators and their research staff can view and edit data on their own subjects only. Furthermore, unique study identification numbers are used to identify subjects on data forms and transmitting subject names or other identifying information over the internet is not permissible.

The central system consists of a Dell PowerEdge 2970 mid-range server. Its features include 4GB of RAM and storage allocated to provide 72GB for the operating system and 145GB for the data. There are 2 quad-core processors installed. For fault tolerance and redundancy the server has five 73GB hard drives.

Operating system installed with Microsoft Windows Server 2003 R2 and SQL Server 2005 database server for processing and housing of clinical data. Microsoft Internet Information Services (IIS) functions as the Web Server for intranet use.

For backup and disaster recovery of the system and data, a dedicated Dell PowerVault LTO-3 tape drive is employed along with Symantec Backup Exec 2010 R3 as the management software. The LTO-3 system has a capacity (per tape) of 400GB native / 800GB compressed. Backup tape media is encrypted to comply with the Federal Encryption Standard, FIPS-140-2 and stored offsite in a secure vault.

The server is located in the SFVAMC Information Research Management Systems (IRMS) server room which has 24-hour surveillance, restricted access and resides within the SFVAMC firewall, providing an extra level of security. This room has air-conditioning units, and provides battery backup in case of a power failure. The server is also kept current with virus protection software and security patches. The server components have been validated through a series of installation, qualification and performance protocols.There are future plans to bring in an additional server machine configured as an application server as well as a library tape system.

Study management is further supported by a Clinical Trial Management System (CTMS) application providing the ability to track many aspects of a clinical trial. Study start-up includes numerous administrative and clinical activities. All of these tasks involve tedious, manual process for collecting and aggregating information from different data sources. The CTMS system consolidates these efforts (i.e. reduce duplications and inconsistencies) and provide efficiencies and cost savings for the clinical operations. Users also manage recruitment outreach activities, track recruitment progress, and search through a pool of potential participants for future studies. The system provides real-time and comprehensive study management metrics to support the day-to-day business operations. This CTMS system is a commercial off-the shelf product that hooks into the research database server for added data integration.

2) General Measures

a) PATIENT SCREENING LOG

Written informed consent will be obtained prior to screening for study eligibility and completion of baseline assessments. All patients who undergo eligibility screening will be listed on the Patient Screening Log to provide information about the number of patients screened.

b) PATIENT LOCATOR INFORMATION
This form includes information about how to contact the participant.

c) BASELINE ASSESSMENTS
Measures will be recorded on several forms and will include demographic information (such as age, gender, race, and ethnicity), work history, medical history, physical examination, laboratory evaluation DSM-IV psychiatric diagnoses, alcohol, substance use, and cigarette smoking history, current medications, and family history..

d) ELIGIBILITY FORM
The listing of inclusion and exclusion criteria will serve as a screening format for eligibility which will be completed following baseline assessments.

e) MAINTENANCE OF THE BLIND
This questionnaire is administered at Week 12 to assess the maintenance of subjects' and physicians' blindness. Subjects are asked to speculate on their assignment to either topiramate or placebo. Each subject's treating physician is also asked to speculate on the subject's assignment to topiramate or placebo.

f) STUDY COMPLETION/TERMINATION FORM
This form is to be administered upon completion of the study (as defined by attending Week 12 visit) or at termination to document the last day of study medication ingestion, number of visits attended and/or reasons for terminating.

g) SUBJECT – END-OF-STUDY QUESTIONNAIRE
This measure is administered at Week 12 to assess the subject's opinion of participation and what was helpful/useful during treatment.

3) Measures of Health/Biological Safety

SUMMARY: Safety evaluations will include: entry medical history and physical examination, weekly vital signs monitoring, weekly breath alcohol concentration (BrAC), weekly CIWA-AD (clinical alcohol withdrawal assessment), weekly monitoring for adverse events, weekly suicide risk assessment, periodic clinical laboratory tests (complete labs including urinalysis at baseline, periodic renal function and liver function tests, and urine pregnancy tests performed every 28 days on women of childbearing potential.

a) MEDICAL HISTORY AND PHYSICAL EXAMINATION
A medical history and physical examination will be completed at baseline during the screening period. Study physicians will screen medical records for a history of glaucoma and kidney stones. This information will be recorded on the physical examination form.

b) CLINICAL LABORATORY TESTS FOR HEALTH AND SAFETY MONITORING
The following tests will be performed by the San Francisco VAMC clinical laboratory.

Clinical laboratory tests at baseline (Screening phase):
Blood samples will be collected for serum chemistry, liver panel (LFTs), renal panel and complete blood count (CBC) and a urine sample will be collected for urinalysis, and, for women – urine pregnancy test.

If AST or ALT are >5 times the upper limit of the normal range, or if serum bilirubin is >2 times the upper limit of normal, these tests will be repeated, and if the repeat tests still exceed these limits, the subject will be excluded.

Clinical laboratory tests for health and safety monitoring throughout the study:
Renal and hepatic panels will be repeated at Visits 6 and 12 for all subjects. Urine pregnancy will be repeated at weeks 4, 8, 12, and 16 for women.

c) BIRTH CONTROL/PREGNANCY ASSESSMENT
Birth Control/ Pregnancy Assessment will be done at baseline/screening at weeks 4, 8, and 12. Any subject who becomes pregnant during participation in the study will be withdrawn. The results will be recorded on a Birth Control/pregnancy Assessment Form.

d) VITAL SIGNS
Vital signs (temperature, heart rate, and blood pressure) will be measured weekly. Weight will be monitored monthly. The results will be recorded on a Vital Signs Form.

e) CONCOMITANT MEDICATIONS
All concomitant medications (prescription or over-the-counter medications) taken at the time of screening as well as those started during the study will be documented on a Concomitant Medication Form completed weekly.

f) CONCOMITANT TREATMENT
All concomitant treatments for mental health and well-being, with a focus on alcohol and substance use and PTSD will be recorded on a monthly basis. At screening, subjects will be asked to report on the history of the mental health treatment. At weeks 4, 8, 12 and 16 they will be asked to report on any new treatments they have started while in the study. Information will be recorded on the Concomitant Treatment form.

g) ADVERSE EVENT (AE) MONITORING
All adverse events that occur between the first study-related procedure and the last study-related procedure will be reported. Serious adverse events occurring within 30 days following the last dose of study medication will be reported to HRPO, USAMRAA and CDMRP within 72 hours of the occurrence or report. Active monitoring of Adverse Events (AEs) will begin as soon as a study participant initiates study treatment, and will continue until the end of study for each participant. AEs will be monitored weekly in two ways:

a. An open-ended question will be asked about presence of any AEs weekly (AE Spontaneous).
b. A checklist of expected topiramate-related AEs will be asked of each participant weekly (AE Checklist).

All Adverse Events will be recorded on the appropriate forms.

h) GLAUCOMA SCREEN
We will screen for glaucoma using the standard method that is currently applied in the clinical care of patients who are being prescribed topiramate for the conditions for which is it already approved. This method involves a clinical assessment utilizing patient history, a brief screen(Ho, Keller et al. 2013), and examination of medical records to screen for glaucoma.

4) Alcohol and Substance Use Measures

a) TIMELINE FOLLOWBACK (TLFB)
Alcohol and drug use will be assessed using the Time-Line Follow-Back (TLFB) (Sobell et al., 1985; Sobell et al. 1992). This is a self-report test which will be performed at baseline/screening and will cover the 12 weeks prior to entry, with particular attention to the 4 weeks immediately preceding entry to the study. In addition, the TLFB will be done weekly for the preceding 7 days at weeks 1-12, and at the week 16 follow-up. The TLFB will be used to calculate percent of days abstinent from alcohol, drinks per drinking day, and percent heavy drinking days. The (TLFB) is a method to assess the quantity of alcohol consumption on a daily basis. With a calendar as a guide, the subject provides a retrospective estimate of daily drinking over a specified period. For this study subjects will estimate their daily drinking for the 28-day period prior to the initial screening and for the 7-day period prior to each weekly visit. The TLFB provides a calendar of the targeted period for recording the number of standard drinks consumed on each day. The TLFB can be used to obtain the number of days on which drinking occurred and the number of drinks per day. Standard Drink Conversions will be used to

standardize all subject reports of alcohol consumption (NIAAA 2007).

The following variables will be derived from the standard drinks consumed per day: 1) Percent Days Abstinent (the number of non-drinking days divided by the number of study days) 2) Percent Heavy Drinking Days (the number of days for which the number of drinks was at least 5 drinks for men and at least 4 drinks for women, divided by the number of study days); 3) Drinks/Day (the number of drinks consumed divided by the number of study days); and 4) Drinks/Drinking Day. The TLFB will be administered in interview format. It takes 5-10 minutes to complete the TLFB for a 28-day period. Interviewers require no clinical expertise but some training. Prior to reviewing alcohol use, the interviewer will prepare the TLFB calendar outlining the time period to be assessed and noting holidays and other general important or newsworthy events that have occurred (e.g., Super Bowl Sunday). During Screening and at each weekly visit thereafter, subjects will be provided with a diary card for recording the number of drinks consumed each day. The diary is intended as a memory aid and interviewers should discuss and verify any information collected on the diary and verify if any days without entries are actually non-drinking days or drinking occurrences that were not recorded. Differences will be discussed with the subject and the site personnel will clarify the number of drinks per day.

Cigarette (Brown et al. 1998) and other non-alcohol substance use will also be collected using the Timeline Followback. Subjects are shown the same calendars used for Alcohol TLFB and asked to use recall to record the number of cigarettes smoked and days of cannabis, cocaine, opiate, and methamphetamine use. Cigarette and other non-alcohol substance use TLFB data will be collected at baseline for the previous 28 day time period. Data will also be collected at each subsequent visit for the time since the last visit.

Purpose: To assess alcohol use frequency and amount on a daily basis, in order to calculate percent of days abstinent from alcohol, drinks per drinking day, and percent heavy drinking days and to assess cigarette and other non-alcohol substance use frequency. Time required for administration: The initial assessment requires 10-15 minutes; subsequent weekly administration takes 5 minutes. Frequency of administration: Baseline and weekly during weeks 1-12 and week 16.

b) FAMILY TREE QUESTIONNAIRE (FTQ)

Family history of alcohol problems is an important variable in alcohol treatment and research. The FTQ is a brief, self-rated questionnaire which provides subjects with a family tree diagram for identifying blood relatives with alcohol problems. The form includes spaces for subjects to describe the relationship of paternal and maternal first-degree (sibling, parents) and second-degree (grandparents, uncles, aunts) relatives to alcohol. Each relative is assigned one of six categories by the subject. The categories are: Never Drank, Social Drinker, Possible Problem Drinker, Definite Problem Drinker, No Relative, Don't Know/Don't Remember. Purpose: To assess family history of alcohol problems. Time Required for Administration: 5 minutes. Frequency of Administration: This test will be administered at the screening visit.

c) ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)

The AUDIT (Saunders et al., 1993) is valid and reliable self-report measure that will be used to screen potential study participants for alcohol use and related problems. The AUDIT assesses items in three domains: alcohol dependence, harmful drinking (drinking that causes direct negative consequences on mental or physical health or social or occupational functioning), and hazardous drinking (drinking that puts one at increased risk for the development of future problems). The assessment consists of 10 multiple-choice and yes-no questions. All of the questions are scored using a 5-point (0-4) Likert scale (items 1 to 8 on a 0-4 scale, and items 9 & 10 are scored 0, 2, 4) and summed to yield a total score of 0-40. A higher score indicates a greater level of dependence. Purpose: To assess alcohol use severity. Time required for administration: The initial assessment requires 2 minutes. Frequency of administration: Baseline and weeks 4, 8, 12, and 16.

d) SHORT INDEX OF PROBLEMS (SIP-2R)

The Short Index of Problems (SIP-2R) (Feinn et al 2003) is a 15-item, self-report measure which provides information on the frequency of various consequences of drinking in the past 3 months based on a 4-point scale. Consequences of drinking that are assessed include financial difficulties, relationship problems, and health problems. This measure was normed on a sample of 1,389 patients with alcohol abuse or dependence seeking treatment for alcohol problems. Studies on the SIP have demonstrated excellent test-retest reliability,

internal consistency, and validity. This measure is conducted at baseline, week 12 and at the last follow-up. Purpose: To provide data for descriptive purposes and a secondary outcome on consequences relating to drinking. Time required for administration: 5 minutes. Frequency of administration: The SIP-2R will be administered at baseline and Wk 12.

e) OBSESSIVE COMPULSIVE DRINKING SCALE (OCDS)

The Obsessive Compulsive Drinking Scale (OCDS) assesses obsessive thoughts and compulsions associated with alcohol craving using a 14-item self-report scale (Anton et al 1995). The OCDS is a modification of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and is designed to measure these thought patterns and behaviors in heavy drinkers. Each question has five possible answers scored on a scale of 0-4. A higher score indicates a greater level of obsessive compulsive drinking. The 14 items will be divided into 4 empirically derived factors (Bohn et al. 1996). The first factor, Drinking Obsessions is composed of 4 variables (items 1-4) that address obsessive thoughts related to drinking. The second factor, Alcohol Consumption, consists of 2 items (items 7 and 8) which evaluate the quantity and frequency of alcohol consumption. The third factor, Automaticity of Drinking contains 5 variables (items 5, 6, 12, 13 and 14) which assess the extent to which drinking was controlled or uncontrolled. The fourth factor, Interference, is comprised of 3 items (items 9, 10 and 11) which evaluate the extent to which drinking interferes with work and social functioning, and the degree to which being prevented from drinking is distressing. The same 14 items will also be summed to produce a total score, an Obsessive Thoughts subscale score, and a Compulsive Drinking subscale score. It takes approximately 5 minutes to complete the OCDS. Purpose: To provide data for descriptive purposes and a secondary outcome relating to drinking. Time required for administration: 5 minutes. Frequency of administration: The OCDS will be administered at baseline screening and weeks 4,6, 8,12, and 16.

f) PENN ALCOHOL CRAVING SCALE (PACS)

The Penn Alcohol Craving Scale (PACS) (Flannery & Pettinati 1999) is a 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. Each question is scaled from 0 to 6. The PACS has been proved to have excellent internal consistency and predictive validity. Purpose: The PACS is a reliable and valid measure of alcohol craving and can predict which individuals are at risk for subsequent relapse. Time required for administration: 5 minutes. Frequency of administration: This test will be administered at baseline screening and weeks 4,6,8,12, and 16.

g) CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT FOR ALCOHOL, DSM-IV VERSION (CIWA-AD)

The CIWA-AD, based on the DSM-IV, is an 8-item questionnaire with which trained staff can quickly and reliably assess the symptoms and severity of alcohol withdrawal (Claassen, 1999). It rates the presence and level of autonomic hyperactivity, tremor, anxiety, hallucinations, agitation, nausea or vomiting and headaches on a 1 to 7 scale. Total score received after rating all symptoms determines the level of withdrawal severity. The CIWA stems from the CIWA-A, a 15 item questionnaire, and the more recent 10 item CIWA-Ar. Scores of 5 or less indicate minimal withdrawal, scores above 5 but less than 12 indicate mild to moderate withdrawal, and scores of 12 or more can signal more severe withdrawal symptoms (Claassen, 1999). The validity and reliability of this test has been demonstrated by Williams et al (2001) and Sellers et al (1991). Purpose: To assess for alcohol withdrawal symptoms. Time required for administration: 1 minute. Frequency of administration: This test will be administered on a weekly basis at baseline, weeks 1-2 and week 16.

h) THOUGHTS ABOUT ABSTINENCE (TAA)

Participants' commitment to abstinence will be assessed with the Thoughts About Abstinence assessment (Hall et al., 1991), modified to assess the participants' thoughts related to alcohol. This self-rated assessment consists of three questions related to alcohol use and relapse, all of which are answerable with a numerical scale (1 through 10). To conclude, participants are asked about their abstinence goal. This measure assesses the participant's motivation with regards to stopping alcohol use and avoiding relapse. In addition, it assesses the client's goal for his/her use ranging from no goal to complete abstinence for life. Purpose: To assess the participant's desire to quit, expected success in quitting and estimated difficulty in avoiding relapse. Time Required for Administration: 2 to 3 minutes. Frequency of Administration: This test will be administered at the screening visit.

i) READINESS TO CHANGE RULER (RTC)

The Readiness to Change Ruler is a brief self-rated assessment of a person's present motivational state relative to changing their drinking habits. Subjects will be asked to mark where they believe they fall on a horizontally oriented scale in which "Never think about my drinking" and "Sometimes I think about drinking less" lie on the left, and "I am already trying to cut back on my drinking" and "My drinking has changed, I now drink less than before" lie on the right. Superseding these categories is a set of numbers from 0 to 10. Subjects will circle the number that corresponds to their current state. The medical staff that conducts Medical Management will perform a follow-up that includes a series of questions based on the number circled. Purpose: To assess a person's readiness and progress with regards to changing their drinking habits. Time Required for Administration: 1 to 2 minutes. Frequency of Administration: This test will be administered at the screening visit.

j) BREATH ALCOHOL CONCENTRATION (BrAC)

The breath alcohol concentration (BrAC) will be measured at each session to detect recent alcohol use. The *Intoximeters Alco-Sensor IV* instrument will be used to measure breath alcohol at each visit to ensure that subjects are not acutely intoxicated. This instrument is approved by the US Department of Transportation for evidential use; it meets and exceeds the federal model specification for traffic enforcement and Omnibus Breath Alcohol Testing (source: Intoximeters Incorporated).

It must be determined that the subject has a BrAC of 0.00% in order to sign the informed consent.

At subsequent visits, if the subject's BrAC is greater than 0.025%, a study physician will assess whether or not the participant may complete the study visit. The participant may be asked to wait until the breathalyzer test is lower, or the participant may be asked to complete the visit at another time. If the participant is deemed incapable of participating in a study visit and is unwilling or unable to remain at the site until their BrAC decreases, then study medication will be dispensed but additional study procedures will not be completed. Breath Alcohol Concentration (BrAC) –will be measured weekly. Study visits that include neurocognitive testing require complete sobriety (0.00%). If a subject's BrAC is greater than 0.00% the subject will wait until BrAC returns to normal or complete the visit on another day. Purpose: To ensure that the subject is sober enough to perform the required study activities. Time required for administration: 1 minute. Frequency of administration: This test will be administered on a weekly basis at baseline, weeks 1-2 and week 16.

k) URINE DRUG SCREEN (UDS)

Urine Drug Screen (UDS): Urine drug testing for opioids, cocaine, cannabis (THC), and amphetamine/methamphetamine. The test will be performed by the SF VAMC Clinical Laboratory. Purpose: To provide data for descriptive purposes, and provide data for exploratory outcomes on substance use other than alcohol. Time required for administration: Collecting the urine sample should take less than 5 minutes. Analysis may take 1 to 3 days (estimate). Frequency of administration: The urine drug screens are conducted at baseline, every 4 weeks during the treatment phase, and at the follow-up visit.

l) ETHYL GLUCURONIDE (EtG)

Ethyl Glucuronide (EtG), is a non-volatile, water-soluble, stable, direct metabolite of ethanol that is currently used in clinical research for alcohol treatment to detect recent alcohol use, up to approximately 80 hours post consumption (Wojcik and Hawthorne, 2007). EtG is considered a sensitive and specific marker that enables detection of small amounts of alcohol in cases where neither traditional biological state markers of alcohol intake nor clinical impression gave an indication for lapse or relapse (Wurst et al., 2003). EtG also validates self-report measures such as TLFB and AUDIT. Purpose: To provide an objective biological measure that detects recent alcohol consumption and verifies self-reported alcohol use within the last 80 hours. Time required for administration: Collecting the urine sample, packing, storing, and shipping should take less than 15 minutes. Once 20 samples have been collected they will be sent to a remote processing center. Test results will be received 1 to 2 weeks from the shipment date (estimate). Frequency of administration: The EtG will be conducted at baseline, all 12 weekly visits, and at the follow-up visit.

m) GAMMA GLUTAMYL TRANSPEPTIDASE (GGT)

GGT is currently the most widely used marker for alcohol consumption. GGT has been found to be elevated in patients with chronic heavy alcohol consumption and in a variety of liver conditions unrelated to drinking and therefore is not specific to alcohol consumption. GGT levels generally rise after heavy alcohol intake that has continued for several weeks. 50-72% of elevated GGT levels can be explained by excessive alcohol consumption (Sillanaukee, 1996). We will measure GGT on a Vitros 950 with a normal range for males of 15-73 U/l and for females of 12-43 U/l. Purpose: To provide an objective biological measure as a secondary measure of alcohol use. Time required for administration: Collecting blood sample should take 5-10 minutes. Lab analysis will take 1-3 days. Frequency of administration: At baseline, and at weeks 6 and 12.

n) EVALUATION OF RISKS SCALES (EVAR-B)
The Evaluation of Risks Scales – B is used to assess risk-taking propensity in military samples (Killgore, Castro et al. 2010). Purpose: To assess the subject's propensity to engage in risky behavior.Time required for administration: 5-10 minutes. Frequency of administration: At baseline, Week 6, 12 and16.

o) SUBJECTIVE HIGH ASSESSMENT SCALE (SHAS)
This scale evaluates 13 subjective feelings of intoxication as changes from baseline(Schuckit, Smith et al. 1997; Schuckit, Tipp et al. 1997). Each question is rated on a Likert-type scale from zero (no effect) to 36 (extreme effect) to assess both positive (e.g., Happy, Relaxed, High, Intoxicated, etc.) and negative (e.g., Nauseated, Clumsy, Confused, etc.) effects that can be associated with alcohol. Purpose: To assess the subjective experience and effects from drinking alcohol. Time required for administration: 5-10 minutes Frequency of administration: At baseline and Weeks 4, 8, 12, and 16.

5) PTSD Measures

a) CLINICIAN-ADMINISTERED PTSD SCALE (CAPS)
The Clinician-Administered PTSD Scale (CAPS) (Blake et al, 1995) is a structured interview for the diagnosis of PTSD and symptom severity, based on the DSM-IV. Its wide use as an outcome measure in clinical research has provided abundant information about CAPS validity, reliability and responsiveness to change with treatment (Blake, 1995). The CAPS provides the format for a careful diagnosis using standardized questions and expanding probes for current and lifetime PTSD symptoms. It simultaneously provides a measure of the intensity and severity of symptoms. King et al (1998) found four correlated but distinct symptom clusters that correspond to DSM PTSD symptom clusters (with distinction between avoidance and emotion numbing). The CAPS instrument is divided into sections based on typical symptom clusters: Criterion A: Exposure to a traumatic event; Criterion B: Re-experiencing; Criterion C: Numbing and avoidance; Criterion D: Hyper-arousal; Criterion E: Chronology; Criterion F: Functional impairment. To score the CAPS we will use the scoring rule that states that a criterion is considered to be present if a subject endorses a symptom with $\geq$ 1 frequency and $\geq$ 2 severity. Purpose: To assess PTSD diagnosis and symptom severity. Time required for administration: 40-60 minutes (Ruggiero, 2003). Frequency of administration: The CAPS will be used at baseline and weeks 6, 12, and 16.

b) PTSD CHECKLIST (PCL)
The PCL (Weathers et al., 1994) is a 17-item self report questionnaire that prompts informants to endorse the level of distress that has co-occurred with each reported PTSD symptom over the prior 30 days. A five point scale is used for informant responding (1 = *not at all, 5 =extremely)* (Ruggiero, 2003). The PCL has been demonstrated to possess good internal consistency, test-retest reliability, convergent validity, and discriminant validity (Ruggiero, 2003). The short administration time also makes it useful in settings where it might need to be administered multiple times. Purpose: To assess PTSD symptom severity. Time required for administration: Approximately 5 minutes (Ruggiero, 2003). Frequency of administration: Administered at baseline screening and at weeks 4, 6, 8, 12, and 16.

6) Psychiatric/Psychological Measures

a) STRUCTURED CLINICAL INTERVIEW FOR DSM-IV-TR, PATIENT EDITION (SCID-I/P)
Alcohol and other substance use disorder diagnoses will be established by administering the Substance Use Disorders (SUDs) diagnostic module of the SCID I/P (First et al., 2001) combined with a review of clinical

records, information from the primary therapist and/or psychiatrist. The SCID-I/P is a clinician-administered, semi-structured interview for use with psychiatric patients. The SCID-I/P is the standard SCID-I designed for research subjects identified as psychiatric patients (Ventura, 1998). The interview begins with an overview section that obtains demographic information, work history, chief complaint and past periods of psychiatric illness, treatment history, and assessments of current functioning with open ended questions to elicit response in the subject's own words. The interview provides required probe questions and suggested follow-up questions. Liberal use of skip-out directions are employed when a subject fails to meet a critical criterion required for a particular disorder. Purpose: To identify eligible potential subjects. Time required for administration: The SUDs module of the SCID-I/P takes approximately 30 minutes to complete. Frequency of administration: This test will be administered at the screening visit.

b) CLINICAL GLOBAL IMPRESSIONS OF IMPROVEMENT AND OF SEVERITY – (CGI-I & CGI-S)

The Clinical Global Impressions (CGI-S and CGI-I) (Guy 1976) is a clinician-rated scale that permits a global evaluation of the subject's improvement over time. At baseline, a CGI-S assessment is performed, in which the investigator rates the severity of a subject's condition on a 7-point scale ranging from 0 (not dependent) to 6 (extremely severe). At subsequent visits, the investigator assesses CGI-S as well as the subject's improvement relative to the symptoms at baseline on a CGI-I, a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Severity scores are cross-sectional whereas global impressions are longitudinal from baseline. Good reliability scores were demonstrated by Dahlke (1992). Purpose: To provide a secondary outcome measure. Time required for administration: 1 to 2 minutes. Frequency of administration: The Clinical Global Impression (Clinician Rated) will be administered at baseline screening and weeks, 4, 8, 12, and 16.

c) PATIENT GLOBAL IMPRESSIONS OF IMPROVEMENT AND OF SEVERITY – (PGI-I & PGI-S)

Patient Global Impression of Improvement (PGI-I) and of Severity (PGI-S) was adapted from the CGI-I and CGI-S scales and permit the patient to directly evaluate disease severity and improvement over time (Rush, First, & Blacker 2008). The PGI-I measures improvement on a 7-point scale with 1 indicating "very much improved" and 7 "very much worse." The PGI-S measures severity of disease ranging from "normal" (1) to "severe" (4) on a 4-point scale. Purpose: This will be an outcome measure indicating how much the subject's symptoms improve as a result of being given topiramate or placebo. Time required for administration: The PGI-I and PGI-S each take 1 to 2 minutes to complete. Frequency of administration: This test will be administered at the screening visit and at weeks 4, 8, 12 and 16.

d) GLOBAL ASSESSMENT OF FUNCTIONING SCALE (GAF)

The Global Assessment of Functioning Scale is a numerical scale (0 through 100) by which mental health clinicians and physicians will rate, subjectively, the social, occupational, and psychological functioning of subjects. Scores are portioned into 10 ranges of functioning. The GAF rating is within a particular decile in within a particular decile if either the symptom severity or the level of functioning falls within the range. In situations where the individual's symptom severity and level of functioning are discordant, the final GAF rating always reflects the worse of the two. The 100 point scale ranges from 1 (Persistent danger of severely hurting self or others, persistent inability to maintain personal hygiene) to 100 (Superior functioning in a wide range of activities; No symptoms). A score of 0 is correlated with inadequate information. Purpose: To assess the functionality of a subject across a variety of categories including social, occupational, and psychological functioning as well as the severity of their symptoms. Time Required for Administration: 5 minutes. Frequency of Administration: This test will be administered at the screening visit.

e) BECK DEPRESSION INVENTORY (BDI)

Depression will be measured with the Beck Depression Inventory (Beck et al., 1961). The BDI is a 21-item, self-report questionnaire that provides a measurement of depression severity. Each item is rated on a four-point scale (absent, mild, moderate, or severe). It has demonstrated high internal consistency and good concurrent validity with other measures of depression (Beck et al, 2000) Purpose: To assess subject depression severity before, during, and after topiramate or placebo treatment. Time required for administration: 5-10 minutes. Frequency of administration: Baseline, 4, 8, 12, 16.

f) BECK ANXIETY INVENTORY (BAI)

The BAI is a 21-item self-report questionnaire designed to evaluate symptoms such as nervousness and inability to relax using a 4-point likert scale (Beck et al., 1988). The BAI has been proven to be a reliable and well-validated measure of anxiety symptoms and is well suited for monitoring change with treatment (Beck, 1988). Purpose: To assess subject anxiety severity before, during, and after topiramate or placebo treatment. Time required for administration: 5 minutes. Frequency of administration: Baseline, 4, 8, 12, 16

g) SUICIDE RISK ASSESSMENT

This measure is the San Francisco V.A Medical Center "Worksheet for Suicide Risk Assessment Note" (SFVAMC, 2009). Purpose: To assess subject anxiety severity before, during, and after completion of HCV treatment. Time required for administration: 5-10 minutes. Frequency of administration: At screen and weekly thereafter.

h) PROFILE OF MOOD STATES (POMS)

The Profile of Mood States (POMS) is a self-report questionnaire to identify and assess transient, fluctuating affective mood states (Mcnair et al, 1971). 60 Six mood states can be derived from this scale: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia and confusion-bewilderment. In addition, the data can be summarized as the total POMS score and can measure the change in mood over time. Subjects complete a 65-item inventory on which adjective variables on mood are rated on a 5point scale from 0 (not at all) to 4 (extremely). The validity and reliability of this test is supported by research, including good test-retest correlations, especially in persons who are disturbed or under stress (Peterson, 1984). Purpose: To measure mood states as a secondary outcome variable. Time required for administration: The questionnaire takes approximately 5 minutes to complete. Frequency of administration: The Profile of Mood States (POMS) will be administered at baseline screening and weeks 6 and 12.

i) PITTSBURGH SLEEP QUALITY INDEX (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval (Buysse et al, 1989). Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score. Clinical and clinimetric properties of the PSQI were assessed over an 18-month period with "good" sleepers (healthy subjects, n = 52) and "poor" sleepers (depressed patients, n = 54; sleep-disorder patients, n = 62). Acceptable measures of internal homogeneity, consistency (test-retest reliability), and validity were obtained. A global PSQI score > 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa = 0.75, p 0.001) in distinguishing good and poor sleepers. The clinemetric and clinical properties of the PSQI suggest its utility both in psychiatric clinical practice and research activities. Purpose: To measure sleep quality as a secondary outcome variable. Time required for administration: 5 to 10 minutes. Frequency of administration: At baseline, and at weeks 6 and 12.

j) INSOMNIA SEVERITY INDEX (ISI)

The Insomnia Severity Index (ISI; Morin, 1993) is a self-rated questionnaire evaluating perceived insomnia severity. The test consists of seven questions that ask respondents to rate the severity of recent problems with sleep onset, sleep maintenance, early waking, and the impact of insomnia on a five-point Likert scale (0=no problem, 4=very severe problem). The total score thereby ranges from 0 to 28, with higher scores indicating more severe insomnia. These scores breakdown into 4 categories: absence of insomnia (0 to 7), mild (8 to 14), moderate (15 to 21), and severe insomnia (22 to 28). Purpose: To assess subject insomnia severity before, during, and after topiramate or placebo treatment. Number of Items: The form includes seven questions with responses ranging from 0 to 4. Time Required for Administration: 1 to 2 minutes. Frequency of Administration: At baseline, and at weeks 6 and 12.

k) DIFFICULTIES IN EMOTIONAL REGULATION SCALE (DERS)

Difficulties in Emotion Dysregulation Scale (DERS; Gratz & Roemer, 2004). The DERS includes six subscales representing the extent to which: (1) emotions are generally understood (clarity – maps onto alexithymia spectrum), (2) emotions are generally attended to (awareness), (3) unpleasant emotions lead to impulsive behaviors (impulsivity), (4) unpleasant emotions are accepted (acceptance), (5) unpleasant emotions interfere

with goal-directed behavior (goals), and (6) unpleasant emotions interfere with strategic use of emotion regulation strategies. All the items can be summed to form a total score, which represents a global composite index of affect regulatory difficulties. As a side note, intense negative emotion and inability to successfully regulate such emotion may be exacerbated by low emotional clarity (i.e., one's understanding of the source and type of emotions they experience). There is some evidence to suggest that successful emotion regulation is dependent on information about the intended target of regulation (clarification about what is being felt moment to moment). This hypothesis has been gaining increasing traction and empirical support, including among veterans with PTSD (Boden, Bonn-Miller, Kashdan, Alvarez & Gross, 2012). Veterans with PTSD may be especially prone to low emotional clarity due to their cognitive dysfunction. Purpose: To assess subject emotional regulation before, during, and after topiramate or placebo treatment and potential relationship to alcohol use and PTSD symptom severity. Number of Items: The form includes six subscales and a total of 36 items. Time Required for Administration: 5 -10 minutes. Frequency of Administration: At baseline, and at weeks 4, 8, and 12.

l) DISTRESS TOLERANCE SCALE (DTS)

Distress tolerance is defined as the capacity to experience and withstand negative psychological states. Distress tolerance is considered a meta-emotion construct that consists of one's evaluations and expectations of experiencing negative emotional states in respect to (1) tolerability and aversiveness, (2) appraisal and acceptability, (3) tendency to absorb attention and disrupt functioning, and (4) regulation of emotions, specifically, the consequent strength of action tendencies. Distress tolerance is a higher-order construct that is manifest in diverse aspects of regulation of affect and behavior Distress tolerance is a common construct in research on affect dysregulation. The construct of distress tolerance has also been invoked in relation to substance use. Alcohol and other substance use may be considered, in part, an emotion focused rather than problem-focused coping strategy. The Distress Tolerance Scale (DTS) is designed to assess the extent to which a person can withstand distress. Purpose: To assess subject's ability to sit with uncomfortable and negative emotion and the extent of distress tolerance is affected by topiramate/placebo, alcohol use, and PTSD symptom severity. Number of Items: The form includes seven questions with responses ranging from 0 to 4. Time Required for Administration: 1 to 2 minutes. Frequency of Administration: At baseline, and at weeks 4, 8, and 12.

m) ALCOHOL PURCHASE TASK (APT)

The Alcohol Purchase Task (APT) was developed as a way to simultaneously measure one's demand for alcohol as well as decision making about alcohol. Briefly, the APT produces a demand curve which is a graphical display of consumption as a function of cost. From this curve, five distinct indices of demand can be calculated: O_{max} (maximum alcohol purchase expenditure), intensity (reported drinking level when alcohol is free), breakpoint (the first price to completely suppress consumption), elasticity (sensitivity of alcohol consumption to increases in cost), and P_{max}, (the point along the demand curve at which consumption moves from being inelastic to elastic). In the APT, a scenario is described in which a participant has the hypothetical opportunity to purchase alcohol at varying cost amounts. The question asked in each scenario is, "how many drinks would you purchase at this cost?" The task has demonstrated sensitivity to intervention; a study of heavy-drinking college students found that several alcohol demand curve indices (i.e., maximum alcohol expenditure, sensitivity of consumption to increasing price) predicted post-intervention alcohol use and frequency of heavy drinking episodes (MacKillop and Murphy, 2007). These results suggest that individuals who demonstrate greater demand for alcohol at baseline (i.e., willing to pay more for a drink, less sensitive to increasing cost) are less likely to change their drinking behavior following an intervention. The APT also has acceptable test-retest reliability (Mackillop et al., 2009). Purpose: To measure decision making about alcohol and test as an exploratory outcome variable. Time to administer: The APT can be completed in approximately 2 minutes. Frequency of administration: The APT will be given at baseline, and at weeks 6, 12, and 16.

7) Neuropsychological Assessment

The neuropsychological battery that will be used in this study was developed to assess performance in the cognitive domains commonly affected by PTSD and alcohol dependence.

The overall battery of neuropsychological tests will take approximately 2 hours, with allowances for breaks. All neuropsychological test data will be scored based on standardized age and when available educational and repeated administration norms, and transformed into z scores for consistency. To assess the impact of training on targeted cognitive domains, and reduce the variability and number of multiple comparisons, z scores of individual neuropsychological tests will be averaged into the Cognitive Domain Scores.

To minimize adverse practice affects, whenever feasible, alternative test forms for repeated testing will be used for repeated administrations.

a) DECISION-MAKING

i) IOWA GAMBLING TASK (IGT)

The Iowa Gambling Task (IGT)[203] is a measure of decision making, considered to be a behavioral manifestation of executive functioning. Subjects are presented with 4 decks of cards on a computer screen and are told that they can win money by picking cards from the most advantageous deck. After each deck selection, subjects are provided feedback as to whether their selection resulted in a "win" or a "loss" and the dollar amount of the win/loss. Its validity has been established in a number of studies examining decision-making abilities with a variety of populations, including substance users. The test generates a continuous score representing the dollar amount that the subject has at the end of the task. Purpose: To test decision-making processes so as to track how it changes over the course of the study and/or examine how it relates to topiramate/placebo, alcohol use and mild PTSD. Number of items: Subjects will choose a single card from 4 decks of cards. This process is repeated approximately 100 times. Time required for administration: 15 to 20 minutes. Frequency of administration: This test will be administered at baseline, as well as weeks 6, 12, and 16.

ii) DELAY DISCOUNTING (DD)

The second behavioral measure of impulsivity will be a delay discounting task of the type used in a number of previous experiments (Baker, Johnson, & Bickel, 2003; Bickel et al., 1999; Coffey et al., 2003; Kirby et al., 1999), using hypothetical rewards. In this task, participants will be asked to choose between a smaller immediate monetary reward and a larger delayed monetary reward. The behavioral principles guiding this task suggest that a pattern of choosing more immediate, smaller rewards over delayed, larger rewards indicates impulsivity (e.g., choice of $25 today over $100 in one month). Following a study conducted in Bickel's laboratory (Baker et al., 2003), the monetary rewards will be in $2 increments between $2 and $100. Delays for the later reward option will be 1 day, 1 week, 1 month, 6 months, 1 year, 5 years, and 25 years. On a computer screen, the participant will be shown, one at a time, hypothetical amounts that could be received immediately, while the hypothetical $100 reward will be displayed continuously. The "delay duration" will indicate the waiting period for the $100 delayed reward. The computer will randomly present each immediate reward amount, one at a time and respondents are asked to choose between each immediate reward or the delayed $100. Immediate reward amounts will be presented randomly. The computer will calculate the indifference point, the point at which delayed and immediate rewards are equally valuable to the participant. The same procedure will be repeated for each of the delay periods. Multiple studies have found that participants do not respond in a systematically different way to real and hypothetical rewards (Baker et al., 2003; Johnson & Bickel, 2002; Madden, Begotka, Raiff, & Kastern, 2003). Purpose: To measure risk-taking as an exploratory outcome variable. Time needed: 10 minutes. Frequency of administration: This test will be administered at baseline, as well as weeks 6, 12, and 16.

b) RISK-TAKING

iii) BALLOON ANALOGUE RISK TASK (BART)

The Balloon Analogue Risk Task (BART; Lejuez et al., 2002, 2003), is a behavioral measure of impulsivity and risk taking developed by Carl Lejuez at the University of Maryland, College Park. Dr. Lejuez's research has shown that riskiness scores on the BART are positively related to self-reports of substance use and health and safety risk behaviors (Lejuez et al., 2002). The BART (Lejuez et al., 2002, 2003) was selected for its merits as a behavioral indicator of impulsivity and its simple, intuitive interface for lower-functioning participants. The

BART displays a computer-generated balloon on the monitor of a desktop computer. The participant uses the click of a mouse to gradually inflate the balloon. Each click adds 5 cents to a temporary bank, the contents of which are not displayed. After each click, the participant has two options, 1) to continue to inflate the balloon at the risk of bursting it and losing all of the money from that balloon, or 2) saving the accumulated money to a permanent bank. Whenever a balloon bursts or the participant chooses to bank money, he or she starts with a new balloon. Participants respond to 30 balloons, each having a different bursting point. With each click, the participant must weigh the potential gain of collecting more money against the potential risk of losing all of the money accumulated with that balloon. The index of riskiness is based on the average number of clicks across balloons. The entire 30-trial task takes approximately 10 minutes to complete.
The instructions to the participant will be as follows: "Throughout the task, you will be presented with 30 balloons, one at a time. For each balloon you can click on the button labeled "Press This Button to Pump Up the Balloon" to increase the size of the balloon. You will accumulate 5 cents in a temporary bank for each pump. You will not be shown the amount you have accumulated in your temporary bank. At any point, you can stop pumping up the balloon and click on the button labeled "Collect $$$." Clicking this button will start you on the next balloon and will transfer the accumulated money from your temporary bank to your permanent bank labeled "Total Earned." The amount you earned in the previous balloon is shown in the box labeled "Last Balloon." It is your choice to determine how much to pump up the balloon, but be aware that at some point the balloon will explode. The explosion point varies across balloons, ranging from the first pump to enough pumps to make the balloon fill the entire computer screen. If the balloon explodes before you click on "Collect $$$," then you move on to the next balloon and all money in your temporary bank is lost. Exploded balloons do not affect the money accumulated in your permanent bank. At the end of the task, you will receive cash in the amount earned in your permanent bank." (Lejuez, 2002, pp. 78-79). Purpose: To measure risk-taking as an exploratory outcome variable. Number of Items: 30 balloons. Time needed: The BART can be completed in approximately 15 minutes. Frequency of administration: The BART will be given at baseline, and at weeks 6, 12, and 16.

c) Measures of COGNITIVE FUNCTIONING

iv) WAIS-III DIGIT SPAN

The WAIS-III Digit Span measures a person's ability to concentrate while manipulating mental mathemateical problems (Wechsler 1997). Purpose: To measure working memory in order to detect neurocognitive deficits that may accompany topiramate or placebo use, mild TBI, and alcohol use. Number of items:. 15 items Time required for administration: 10-15 minutes Frequency of administration: This test will be administered at baseline, as well as weeks 6, 12, and 16.

v) WAIS-III ARITHMETIC

The WAIS-III Arithmetic measures a person's attention, concentration and mental control(Wechsler 1997). Purpose: To measure working memory in order to detect neurocognitive deficits that may accompany topiramate or placebo use, mild TBI, and alcohol use. Number of items: 20 items Time required for administration: 10-13 minutes Frequency of administration: This test will be administered at baseline, as well as weeks 6, 12, and 16.

vi) CONTROLLED ORAL WORD ASSOCIATION (COWA):

The Controlled Oral Word Association is another assessment used to measure the performance of complex attention and executive functioning; specifically, verbal fluency. During the test the examinee is asked to generate words that begin with a specified letter for one minute (phonemic fluency); and to generate words that belong to a specified category (semantic fluency)[98] Purpose: To measure verbal fluency in order to detect neurocognitive deficits that may accompany topiramate or placebo use, PTSD, and alcohol use. Number of items: This test consists of three letter associations as well as two category associations. Time required for administration: 10 minutes. Frequency of administration: This test will be administered at baseline, as well as weeks 6, 12, and 16.

vii) HOPKINS VERBAL LEARNING TEST (HVLT)

Performance on Verbal and Visual Memory tests will be assessed with Hopkins Verbal Learning Test (HVLT-R)[99], requiring participants to learn 12 words after 3 learning trials and to recall them after 25 minutes. The Hopkins Verbal Learning Test (Brandt, 1991) was developed to briefly assess verbal recall and recognition. It consists of three learning/free-recall trials followed by a yes/no recognition trial (Rasmusson, 1995). Test stimuli are 12 words, four from each of three semantic categories. In the recognition trial, the 12 target words are interspersed among 12 distractor words. Six distractor items are high frequency exemplars of the same semantic categories as the target words, and six more are from other semantic categories. Because of these features the HVLT is well suited to repeated assessments (e.g., drug trials, tracking recovery from traumatic head injury or ECT) or where time constraints allow for only a brief assessment of new learning. The domains tested by the Hopkins are verbal recall and recognition (memory). Test–retest correlations of the HVLT are similar to other verbal memory tests, like the Logical Memory subtest of the Wechsler Memory Scale—Revised and the California Verbal Learning Test (Kuslansky, 2004). Other studies of the HVLT support its alternate form and test–retest reliability and its construct and content validity. The HVLT's reliability and validity has also been demonstrated in patients with head injury, schizophrenia, and dementia (Kuslansky, 2004). Purpose: To measure verbal memory and recall in order to detect neurocognitive deficits that may accompany topiramate or placebo use, PTSD, and alcohol use. Number of items: 12 words are shown to subject 3 times (learning trial / free recall). This is followed by a recognition trial (Rasmusson, 1995). Time needed: 10 minutes or less (Rasmusson, 1995). Frequency of administration: This test will be administered at baseline, as well as weeks 6, 12, and 16.

viii) TRAIL MAKING TEST (TMT) PARTS A & B

The Trail Making Test, or TMT, was created as part of the Army Individual Test Battery (1944). Since then it has been widely used as an easily administered test of visual conceptual and visuomotor tracking (Spreen, 1998). Since it was developed by the U.S. Army, it is in the public domain and can be reproduced without permission. The test is given in two parts, A and B. The subject is first asked to draw lines connecting consecutively numbered circles on one work sheet (Part A), and then they are asked to connect the same number of consecutively numbered and lettered circles on a different worksheet, alternating between the two sequences (Part B). The subject is asked to connect the circles as fast as they can, without lifting the pencil from the paper. Scores are based on the amount of time the subject needs to complete the test. The most common scoring method is the one created by Reitan (undated) in which the examiner points out errors as they occur, so that the subject can complete the test without errors. Then the score is based on time alone (Lezak, 1995). The domain tested by the TMT is tests complex visual scanning with a motor component (Shum, et al, 1990). Scores on the TMT are reliably sensitive to overall intelligence, neurological impairment, and age (Brown, 2006), and the TMT has been shown to be effective at discriminating between Vietnam combat veterans with and without PTSD (Beckham, 1998). It also has excellent interrater reliability (Brown, 2006). Purpose: To measure neurocognitive deficits that may accompany topiramate or placebo use, PTSD, and alcohol use. Number of items: Subject connects 25 encircled numbers in part A, and another 25 encircled numbers in part B. Time needed: A cutoff time of 300 seconds is generally used to discontinue test administration and is therefore the typical maximum score (Bowie, 2006). Frequency of administration: Will be administered at baseline, then again at week 6, 12, and 16.

ix) WECHSLER TEST OF ADULT READING (WTAR):

Intellectual functions estimate will be assessed at baseline with Wechsler Test of Adult Reading- WTAR: The purpose of the WTAR is an estimation of pre-morbid intellectual ability. The examinee is asked to read a list of 50 words that have a typical grapheme to phoneme translations. Reading recognition is relatively stable in the presence of cognitive decline associated with brain injury[101]. Purpose: To gain a baseline estimation of intellectual functioning in order to examine how it relates to topiramate or placebo, PTSD, and/or alcohol use. Number of items: The examinee is asked to read out loud 50 words which are compared to given pronunciations and tallied for a total score of words read correctly. Time required for administration: 5 to 10 minutes Frequency of administration: The test will be administered at baseline.

d) IMPULSIVITY Measures

x) STROOP INHIBITION:

The Stroop Inhibition[98] is another assessment used to measure the performance of complex attention and

executive functioning; specifically, inhibition of automatic responding. The Stroop Inhibition (time and error score)[98] in which words are printed in dissonant ink color, and participants are instructed to name the color of the ink instead of the automatic response of reading the word. Purpose: To measure inhibition of automatic responding, an executive functioning task that is thought to be affected by alcohol use and PTSD. Number of items: There are three, single page forms that subjects will be instructed to read from. These sheets consists of a Word Page with color words printed in black ink, a Color Page with 'Xs' printed in color, and a color-Word Page with words from the first page printed in colors from the second page (the color and the word do not match).Time required for administration: 5 minutes. Frequency of administration: This test will be administered at baseline, as well as weeks 6, 12, and 16.

xi) BARRATT IMPULSIVENESS SCALE-II (BIS-II)

The Barratt Impulsiveness Scale is a widely-used self-report measure of impulsive behaviors. It has been consistently correlated with other self-report measures of impulsivity, and has been normed on a variety of populations, including substance abusers. Cronbach's alpha ranged from .79 to .83.[89] Validity has been established on veteran populations as well.[197] The BIS yields a continuous score, with higher scores indicating more impulsivity. Purpose: To measure impulsivity over the course of the study to assess how it relates to topiramate or placebo, alcohol use and/or PTSD symptom severity. Number of items: One form for every administration of the test. Time required for administration: 5 to 10 minutes. Frequency of administration: This test will be administered at baseline, as well as weeks 6, 12, and 16.

xii) STOP-SIGNAL TASK

The Stop Signal Task is a test designed to provide a measure of an individual's ability to inhibit an impulse. During the test, subjects are instructed to respond as fast as they can to symbols such as letters or arrows presented on a computer screen. An auditory tone, which indicates to the participant that they are to withhold their response, accompanies a portion of these symbols. The tone occurs at various latencies after the appearance of the symbol on the computer and is randomized for each participant.
The SSRT, stop signal reaction time, is an estimation of the time an individual needs to stop their usual behavior (Striking a key every time they see the corresponding symbol) in response to the stop signal.
Purpose: To measure the ability of a subject to inhibit thought and action over the course of the study in order to examine how inhibition relates to topiramate or placebo, alcohol use and PTSD. Time required for administration: 20 minutes. Frequency of administration: This test will be administered at baseline, as well as weeks 6, 12, and 16.

e) ALCOHOL APPROACH BIAS ASSESSMENT

xiii) ALCOHOL APPROACH TASK

A non-training version of the Alcohol-AAT will measure automatic approach tendency toward alcohol at baseline and Week-4. This differs from our training AABM in that every picture will be presented in both formats (push landscape, pull portrait). The task starts with 10 practice trials showing neutral objects, followed by 80 test trials. A standardized d-score is calculated which represents differences in reaction time for pushing vs. pulling[209]. Negative values indicate less attentional bias[209]. Number of items:90 Time required for administration: 20 minutes Frequency of administration: Weeks 0, 8, 12.

8) Genetic Testing

Approximately 2 teaspoons of blood will be drawn by SFVAMC clinical laboratory personnel or at the VA Clinical Research Center from a vein in the participant's arm. We will genotype participants for genes thought important in the initiation and persistence of alcohol use disorders, such as GRIK1, COMT, and OPRM1. We will look at these specific genes and their potential associations with topiramate treatment. DNA will be isolated from the blood and stored at the UCSF DNA Bank. Genetic testing is optional and refusal to participate will not exclude individuals from participating in the study. All blood tests will be performed only after a full study consent is completed. All blood samples will be coded with a subject ID, and only investigators/key personnel listed on this research protocol will have access to the key.

9) TBI Measures

a) NEUROBEHAVIORAL SYMPTOM INVENTORY (NSI):

In accordance with the recommendation of the Review Committee, we are specifying the inclusion of the Neurobehavioral Symptom Inventory (NSI) as a measure to quantify symptoms associated with mild traumatic brain injury. The NSI evaluates common complaints associated with mild TBI and post-concussive syndrome. The NSI asks patients to rate how much various symptoms have disturbed them in the last two weeks. While it is not a diagnostic test, the constellation of symptoms has been validated for mild TBI, and the NSI is useful in developing a clinical profile (Cicerone & Kalmar, 1995; Meterko et al., 2012). Cicerone and Kalmar developed this 22-item self-report inventory of symptoms commonly observed among patients with mild TBI. The NSI, based on the Cicerone and Kalmar tool, is utilized by the Veterans Administration in the evaluation of returning OEF/OIF veterans. The 22 items of the NSI are embedded within the VA's Secondary TBI Evaluation that is conducted for all veterans entering the VA who have not been previously diagnosed with TBI, but who screen positive for possible TBI.
We will analyze the results to detect both within-group changes in the Topiramate arm of the study as well as between-groups differences between the Topiramate and Placebo groups over the course of the study.
Purpose: To quantify symptoms associated with mild traumatic brain injury. Time Required for administration: 5-10 minutes. Frequency of administration: The NSI will be administered at baseline and weeks 4, 8, 12, and 16.

b) VA LEVEL 2 TBI EVALUATION

The VA Level 2 TBI Evaluation is an assessment of traumatic brain injury and will be used to validate the occurrence of a TBI and the corresponding severity. Purpose: To validate the occurrence of a mild traumatic brain injury. Time Required for administration: 20 minutes. Frequency of administration: The Level 2 TBI Evaluation will be administered at baseline.

I. Weekly Visit Schedule

1) Screening Phase: Prescreening, Consent, Screening and Baseline Assessments

Each subject's participation in the study begins with the Screening Phase, consisting of approximately 3 visits over roughly 1 week, during which subjects are evaluated for entry into the study. After the subject passes the brief Prescreening Questionnaire (done in person or over the telephone), a consent form will be given to the subject to read and an oral explanation of the procedures will be given allowing the subject time to ask questions and consider study participation. Once the subject has agreed to participate in the study, a signed and dated informed consent will be obtained before any study-related procedures are performed. Each subject will be provided a copy of his/her signed and dated informed consent.

a) PRESCREENING

-Prescreening Questionnaire done in person or over the telephone

b) INFORMED CONSENT

See Section D.3.c.

c) MEASURES

The following baseline measures and procedures will occur during approximately 3 visits over roughly 1 week and take approximately 4.5 to 7 hours to complete.

These measures are summarized in *Table 1 – Schedule of Measures*, at the end of this document.

-Prescreen CPRS and Phone
-Demographic Questionnaire
-Fill in patient locator information form
-Review inclusion/exclusion criteria using the eligibility form
-Review medical history
-Review medical record for evidence of current PTSD treatment.
-Concurrent medications form

-Concurrent Treatment form
-Adverse Event Forms – spontaneous and checklist
-Structured Clinical Interview for DSM-IV (Patient Edition) (SCID-IP)
-Timeline Followback (TLFB) information for alcohol use for the past 90 days; cigarette and other non-alcohol substance use for the past 30 days.
- Alcohol Use Disorders Identification Test (AUDIT)
-Obsessive Compulsive Drinking Scales (OCDS)
-Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD)
-Penn Alcohol Craving Scale (PACS)
-Short Index of Problems (SIP-2R)
-Family Tree Questionnaire (FTQ)
-Thoughts About Abstinence (TAA)
-Readiness to Change Ruler (RTC)
-Alcohol Purchase Task (APT)
-Evaluation of Risks Scales (EVAR)
-Subjective High Assessment Scale (SHAS)
-Clinician-Administered PTSD Scale (CAPS)
-PTSD Checklist (PCL)
-Neurobehavioral Symptom Inventory (NSI)
-2nd Level TBI Evaluation
-Clinical Global Impression of Improvement and of Severity (CGI-I & CGI-S)
-Patient Global Impression of Improvement and of Severity (PGI-I & PGI-S)
-Beck Depression Inventory (BDI)
-Beck Anxiety Inventory (BAI)
-Suicide Risk Assessment
-Profile of Mood States (POMS)
-Global Assessment of Functioning (GAF)
-Pittsburgh Sleep Quality Index (PSQI)
-Insomnia Severity Index (ISI)
-Difficulties in Emotion Regulation Scale (DERS)
-The Distress Tolerance Scale (DTS)
-Trail Making Test A & B (TMT A and B)
-Iowa Gambling Task (IGT)
-Hopkins Verbal Learning Test (HVLT-R)
-Delay Discounting (DD) on computer
-Balloon Analogue Risk Task (BART) on computer
-Auditory Consonant Trigrams (ACT)
-Controlled Oral Word Association (COWA)
-Stroop Inhibition
-Wechsler Test of Adult Reading (WTAR)
-Barrett Impulsivity Scale (BIS-II)
-Stop Signal Task (SST)
-WAIS-III Digit Span
-WAIS-III Arithmetic
-Alcohol Approach Task (AAT)

d) PROCEDURES

-Perform physical examination
-Utilize patient history and examine medical records to screen for glaucoma and kidney stones.
-Lab Tests (GGT, CBC, renal panel, hepatic panel including AST [SGOT])
-Assess birth control method and perform urine pregnancy test (women only)
-Obtain vital signs (temperature, weight, heart rate, blood pressure sitting and standing)
-Breath Alcohol Concentration (BrAC)
-Urine Drug Screen (UDS) testing for cocaine, amphetamines, THC, benzodiazepines, methadone and opiates.

-Ethyl Glucuronide (EtG) verifying self-reported alcohol use in the last 72 hours.
-Conduct Medical Management Alcohol Counseling (MM) Session
-Review Medical Event Monitoring System (MEMS)
-Medication Dispensing Form, dispense Medication
-Drug Accountability

Subjects will receive $25 at each screening visit for a potential total of $75 for the entire screening period.

Following completion of Screening Phase: Review inclusion/exclusion criteria using the Eligibility Form and proceed to the Treatment Phase.

2) Treatment Phase

Randomization assignment occurs at the week 1 visit.

a) WEEKS 1, 2, 3, 5, 7, 9, 10, 11

The measures and procedures collected and performed at these visits requires approximately 1 to 1.5 hours, the shortest amount of time relative to other visits. As such, subjects will receive $20 at completion of each visit.

•Measures
-Concurrent medications
-Adverse event form – spontaneous and checklist
-Timeline Followback (TLFB) information for alcohol use, cigarettes, and other non-alcohol substance use for the past 7 days
-Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD)
-Suicide Risk Assessment
-Alcohol Approach Task (AAT) (Week 11 only)

•Procedures
-Obtain vital signs (temperature, heart rate, blood pressure sitting and standing)
-Breath Alcohol Concentration (BrAC)
-Ethyl Glucuronide (EtG) verifying self-reported alcohol use in the last 72 hours.
-Conduct Medical Management Alcohol Counseling (MM) Session
-Review Medical Event Monitoring System (MEMS)
-WEEK 1 Only: Randomized assignment to study medication
-Dispense study medication
-Medication Dispensing Form
-Drug Accountability

b) WEEKS 4, 8

The intermediate visits occuring on weeks 4 and 8 include some measures and procedures that were originally collected at baseline/screening to ensure safety and allow for subsequent points of comparison. These visits are estimated to take between 2 to 2.5 hours to complete and pay at a rate of $30 per completion.

•Measures
-Concurrent Medications Form
-Concurrent Treatments Form
-Adverse event form – spontaneous and checklist
-Timeline Followback (TLFB) information for alcohol use, cigarettes, and other non-alcohol substance use for the past 7 days
-Alcohol Use Disorders Identification Test (AUDIT)
-Obsessive Compulsive Drinking Scales (OCDS)
-Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD)
-Penn Alcohol Craving Scale (PACS)
-Subjective High Assessment Scale (SHAS)

-PTSD Checklist (PCL)
- Neurobehavioral Symptom Inventory (NSI)
-Clinical Global Impression of Improvement and of Severity (CGI-I & CGI-S)
-Patient Global Impression of Improvement and of Severity (PGI-I & PGI-S)
-Beck Depression Inventory (BDI)
-Beck Anxiety Inventory (BAI)
-Suicide Risk Assessment
-Pittsburgh Sleep Quality Index (PSQI)
- Insomnia Severity Index (ISI)
-Difficulties in Emotion Regulation Scale (DERS)
-The Distress Tolerance Scale (DTS)

•Procedures
-Obtain vital signs (temperature, weight, heart rate, blood pressure sitting and standing)
-Assess birth control method and perform urine pregnancy test (women only)
-Breath Alcohol Concentration (BrAC)
-Urine Drug Screen (UDS) testing for cocaine, amphetamines, THC, benzodiazepines, methadone and opiates.
-Ethyl Glucuronide (EtG) verifying self-reported alcohol use in the last 72 hours.
-Medical Management Alcohol Counseling (MM)
-Medical Event Monitoring System (MEMS)
-Dispense study medication
-Medication Dispensing Form
-Drug Accountability

c) WEEKS 6, 12

The longest visits take place on weeks 6 and 12 and reimburse subjects $35 in return. The procedures and measures at week 6 will take approximately 3 to 4 hours to complete and approximately 3.5 to 5 hours for visit 12.

•Measures
-Concurrent Medications Form
-Concurrent Treatment Form (Week 12 Only)
-Adverse Event Forms – spontaneous and checklist
-Alcohol Purchase Task (APT)
-Penn Alcohol Craving Scale (PACS)
-Obsessive Compulsive Drinking Scales (OCDS)
-Timeline Followback (TLFB) information for alcohol use, cigarettes, and other non-alcohol substance use for the past 7 days
-Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD)
-Evaluation of Risks Scales (EVAR)
-Clinician-Administered PTSD Scale (CAPS)
-PTSD Checklist (PCL)
-Suicide Risk Assessment
-Profile of Mood States (POMS)
- Insomnia Severity Index (ISI) (Week 12 Only)
-Subjective High Assessment Scale (SHAS) (Week 12 Only)
-Difficulties in Emotion Regulation Scale (DERS) (Week 12 Only)
-The Distress Tolerance Scale (DTS) (Week 12 Only)
-Trail Making Test A & B (TMT A and B)
-Hopkins Verbal Learning Test (HVLT-R)
-Auditory Consonant Trigrams (ACT)
-Delay Discounting (DD) on computer
-Balloon Analogue Risk Task (BART) on computer
- Iowa Gambling Task (IGT)

-Controlled Oral Word Association (COWA)
-WAIS-III Digit Span
-WAIS-III Arithmetic
-Stroop Inhibition
-Barrett Impulsivity Scale (BIS-II)
-Stop Signal Task (SST)
-Wechsler Test of Adult Reading (WTAR)

•Procedures
-Obtain vital signs (temperature, weight, heart rate, blood pressure sitting and standing)
-Breath Alcohol Concentration (BrAC)
-Lab Tests (GGT, CBC, renal panel, hepatic panel including AST [SGOT])
-Ethyl Glucuronide (EtG) verifying self-reported alcohol use in the last 72 hours.
-Medical Management Alcohol Counseling (MM) (Week 6 Only)
-Review Medical Event Monitoring System (MEMS)
-Dispense study medication (only week 6)
-Medication Dispensing Form
-Drug Accountability

Note: the week 12 visit includes an additional 16 assessments and requires an extra 45 minutes to an hour to complete. They include the following:
-Assess birth control method and perform urine pregnancy test (women only)
-Measure weight
-Urine Drug Screen (UDS) testing for cocaine, amphetamines, THC, benzodiazepines, methadone and opiates.
-Alcohol Use Disorders Identification Test (AUDIT)
-Obsessive Compulsive Drinking Scales (OCDS)
-Penn Alcohol Craving Scale (PACS)
-Neurobehavioral Symptom Inventory (NSI)
-Short Index of Problems (SIP)
-PTSD Checklist (PCL)
-Clinical Global Impression of Improvement and of Severity (CGI-I & CGI-S)
-Patient Global Impression of Improvement and of Severity (PGI-I & PGI-S)
-Beck Depression Inventory (BDI)
-Beck Anxiety Inventory (BAI)
-Maintenance of the Blind
-Study Completion/Termination Form
-Subject – End-of-Study Questionnaire

3) Follow-up Phase

The last visit, or follow-up, will take place on week 16. Participants will receive $35 for their time and visit will last between 1.5 to 2 hours.

•Measures
-Concurrent Medications Form
-Concurrent Treatments Form
-Adverse Event Forms – spontaneous and checklist
-Timeline Followback (TLFB) information for alcohol use, cigarettes, and other non-alcohol substance use for the past 28 days
- Alcohol Use Disorders Identification Test (AUDIT)
-Obsessive Compulsive Drinking Scales (OCDS)
-Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD)
-Evaluation of Risks Scales (EVAR)
-Penn Alcohol Craving Scale (PACS)
-Neurobehavioral Symptom Inventory (NSI)

-Alcohol Purchase Task (APT)
-Subjective High Assessment Scale (SHAS)
-Short Index of Problems (SIP)
-PTSD Checklist (PCL)
-Clinical Global Impression of Improvement and of Severity (CGI-I & CGI-S)
-Patient Global Impression of Improvement and of Severity (PGI-I & PGI-S)
-Beck Depression Inventory (BDI)
-Beck Anxiety Inventory (BAI)
-Pittsburgh Sleep Quality Index (PSQI)
- Insomnia Severity Index (ISI)
-Trail Making Test A & B (TMT A and B)
-Delay Discounting (DD) on computer
-Balloon Analogue Risk Task (BART) on computer
-Auditory Consonant Trigrams (ACT)
-Controlled Oral Word Association (COWA)
- Iowa Gambling Task (IGT)
-Hopkins Verbal Learning Test (HVLT-R)
-Stroop Inhibition
-Barrett Impulsivity Scale (BIS-II)
-Stop Signal Task (SST)

•Procedures
-Obtain vital signs (temperature, weight, heart rate, blood pressure sitting and standing)
-Breath Alcohol Concentration (BrAC)
-Urine Drug Screen (UDS) testing for cocaine, amphetamines, THC, benzodiazepines, methadone and opiates.
-Ethyl Glucuronide (EtG) verifying self-reported alcohol use in the last 72 hours.

D.4. STATISTICAL PLAN AND DATA ANALYSIS

The general data analytic approach for each outcome is an intent-to-treat analysis based on a linear mixed effects model for repeated measures, with random intercepts to account for within-subjects correlations over time. Treatment Group, Time (weeks in treatment), and the Group by Time interaction are the predictors. The baseline measure of each outcome variable is included as a covariate. A treatment effect is indicated by a significant Group by Time interaction, with the Topiramate group showing greater end of trial improvement after covarying for baseline measures. A likelihood ratio test (LRT) will be used to compare the random intercept only model with a model containing both random intercepts and random coefficients for Time. If the LRT is significant, the random coefficient model will used, otherwise the more parsimonious random intercept only model will be used. The proposed study has primary, secondary, and exploratory outcomes. Assumptions of the analyses, such as linearity and normality, will be checked for each outcome variable. Log or other appropriate transformations will be applied if needed.

D.4.a. Primary Outcome Measure: The primary outcome measure will be the difference in percent of heavy drinking days (PHDD) per week between the topiramate treatment and the placebo control groups over the course of the 12-week trial as measured by the Timeline Followback. Although controversy remains regarding the optimal outcome measure in alcohol treatment clinical trials, the choice of PHDD as the primary outcome is based on its endorsement by a recent NIAAA consensus conference (Falk et al. 2010) and its increasing use in clinical trials (Gastfriend et al. 2007; Garbutt et al. 2010; Pettinati et al. 2011).

1) Primary Hypothesis

The primary hypothesis is that topiramate treatment will be more efficacious than placebo in reducing the Percent Heavy Drinking Days (PHDD) over the course of the 12-week trial, as indicated by a lower baseline-adjusted PHDD score in the Topiramate group compared to Control group during the 12 week treatment phase.

2) Data Analytic Technique for Primary Outcome

The primary data analytic technique will be a linear mixed model used to estimate mean within-subjects change in the primary outcome over time in the topiramate group. Gender, age, hazardous or harmful alcohol use diagnosis, and presence or absence of abstinence from alcohol in the 4 days prior to study entry will be entered as covariates in the model. Time period will be treated as a repeated effect, with correlations between time periods within subjects modeled by an unstructured correlation matrix. Assumptions of the model will be tested and any required modifications will be performed. For example, we will test for non-linear effects of time and for normality of residuals. If residuals are non-normally distributed, we will rely on bootstrap estimates of standard errors for conducting statistical tests.

Commented [DoVA1]: Still linear mixed model?

Commented [v2]: Will we want to change from mean to count model?

3) Power Analyses for the Primary Outcome

In order to perform the power analysis for the primary hypothesis, we conducted an unblinded interim analysis of the first 24 subjects with alcohol dependence and PTSD enrolled in the PI's current pilot study, Topiramate Treatment of Alcohol Dependence in PTSD (Batki NCT01087736). Based on these data, we expect the mean difference in PHDD between treatment and control groups over the 12 weeks of the study, adjusted for baseline PHDD, to be approximately 11.1%. The trend over time was approximately linear on a log scale, and therefore we estimated power based on a linear mixed model using the log-transformed outcome data. We calculated a between-subjects variance of 0.32 and a residual variance of 0.20, both on the log scale. Based on these parameters, we estimate that n=75 per group (total n=150) will yield a power of over 80% at alpha=.05 to detect a significant effect on our primary outcome. Power calculations were derived from simulations using PASS 2008 software.

D.4.b. Secondary outcome measures:

1) Secondary Hypotheses

Secondary hypothesis (2.1): Topiramate treatment -- combined with Medical Management alcohol counseling and added to ongoing PTSD treatment as usual --will be associated with a significant reduction in PTSD symptoms from baseline to the end of the trial, as measured by the PTSD Checklist (PCL) ; and there will be a significant effect of the treatment group, with the topiramate treatment group showing a greater reduction in PCL scores compared to placebo controls.

Secondary hypothesis (2.2): Topiramate treatment -- combined with Medical Management alcohol counseling and added to ongoing PTSD treatment as usual --will be associated with significant reductions in other alcohol use measures (drinking days/week, drinks per drinking day, alcohol craving, and urine Ethyl Glucuronide [EtG]) from baseline to end of treatment; and there will be a significant effect of the treatment group, with the topiramate treatment group showing a greater reduction in scores on various alcohol use measures compared to placebo controls.

2) Data Analytic Technique for the Secondary Outcome

Secondary hypothesis (2.2) and (2.3) will be tested with a linear mixed model identical to that for the primary hypothesis, with a separate mixed model for each outcome variable. Adjustments for multiple comparisons will be made separately for the separate families of secondary outcomes, i.e. alcohol measures and PTSD measure, using a modification of the Bonferroni method for correlated outcomes[98]. Power estimates for the other drinking variables based on our preliminary data, as described for PHDD, indicate minimum power of 80% to detect improvements in these variables with n = 150 subjects.

Commented [DoVA3]: Still linear mm?

D.4.c. Exploratory outcomes/exploratory hypotheses:

1) Exploratory Hypotheses

The *exploratory hypotheses are:*

(3.1) High impulsivity, high risk-taking, and poor decision making at baseline will be associated with higher levels of alcohol use at baseline and over the course of the study;

(3.2) Reductions in alcohol use will be associated with reductions in impulsivity, risk taking and improvement in decision-making;

(3.3) Topiramate will be associated with greater reductions in impulsivity and risk-taking, but also with greater impairment of verbal fluency and memory than placebo.

D.5. DATA SHARING PLAN

Human subject data will be shared with other investigators within the limits of HIPAA and other patient confidentiality requirements (including UCSF and SFVAHCS regulatory practices), including the removal of all patient identifiers from all source documents and the use of unique patient identification numbers. Prior approval will be obtained from collaborating investigators, research sponsors, and/or other contributors before sharing if proprietary information or products are involved. This may include HIPAA authorization and informed consent from study participants, as well as a Data Use Agreement between the either the San Francisco Veterans Affairs Medical Center, UCSF, and the data recipient. The Data Use Agreement will prohibit the recipient from identifying or re-identifying any individual whose data are included in the data set. Datasets will be stripped of patient identifiers and other information that might allow inadvertent identification due to unusual data elements. Researchers will be asked to sign a data use agreement that provides at a minimum for commitments to: (1) use the data only for research purposes and not to identify any individual participant; (2) secure the data using appropriate computer technology; (3) not distribute the data to third parties; (4) use the data only for approved specific research aims; and (5) sound scientific research questions; and (6) agree to give proper credit to the funding agency and the investigators who collected the data in any publications resulting from the data. Only *de-identified, anonymized data will be made available in electronic machine/computer readable form (i.e., CSV)*, and all sharing of data will comply with UCSF and SFVAHCS regulations. In the final year of this project we will begin preparation of the data set for sharing, which includes the standard data cleaning and quality control that is ongoing throughout the project. When appropriate, an agreement may be reached with the recipient prior to sharing, establishing what the data would be used for and assuring that only non-identified, aggregate data would be presented by the recipient.

D. 6. STUDY LIMITATIONS/POTENTIAL PROBLEMS: Traditionally, recruitment, retention, missing data, and safety issues have been the most difficult hurdles facing clinical trials in alcohol used disorders. We believe that our research team is demonstrating a high level of success in recruiting and retaining subjects in treatment, with 83% of subjects completing the PI's pilot trial of topiramate. Similarly, there has been little missing data, with 88% of weekly study visits attended. Moreover, the use of a mixed-effects model allows for the use of all available data in model estimation. Finally, human subject safety is always the prime concern in trials such as these. To date, there is no signal indicating lack of safety in our pilot controlled trial of topiramate, and the study team has developed a comprehensive human subject protection plan.

D.7. TIME SEQUENCE

The study is expected to last 60 months. Months 1-4 will be used to prepare for the start of the study. Recruitment will take place from Months 5 - 50, accruing subjects at a rate of 3-4 per month and totaling 150 enrolled subjects. Treatment phase will begin at Month 5 and extend through Month 53; follow-up phase ends Month 54. Months 55-60 will cover completion of data analysis, preparation of products, publications, and presentations.

E. HUMAN SUBJECTS RESEARCH CONCERNS

E.1. PROTECTION OF HUMAN SUBJECTS

The PI will be responsible for following adverse event reporting requirements as outlined below in the protocol. These responsibilities include reviewing the accuracy and completeness of all adverse events reported; compliance with IRB policies for reporting adverse events and serious adverse events; reporting any safety issues to the IRB; and closely monitoring research volunteers at each study visit and telephone contact for any new Adverse Events (AEs) or Serious Adverse Events (SAEs).

a. Risks to Subjects

1) Description of Human Subjects Involvement

We propose a pilot prospective, double-blind, placebo-controlled clinical trial of topiramate treatment to reduce alcohol use and PTSD symptoms in veterans with PTSD and alcohol dependence. Because this is a pilot study with limited resources, duration, and sample size, the primary aim will be to measure the pre-post change in alcohol use within the topiramate arm of the study. The secondary aim will be to measure the

between-groups difference in alcohol use over the course of the study comparing the topiramate and placebo arms in order to attempt to detect a signal indicating differential efficacy of topiramate and placebo. Other secondary aims will include obtaining additional measurements of alcohol use, measures of PTSD symptoms, and measures of impulsivity and risk-taking over the course of the pilot trial. To achieve these aims, we will conduct a pilot prospective, parallel groups, randomized, double-blind, placebo-controlled flexible-dose clinical trial of topiramate in 32 veterans with PTSD and alcohol dependence. The primary treatment outcome will be the Percent Days of Heavy Drinking (PHDD) of alcohol. A heavy drinking day is defined using NIAAA (2007) criteria: any day with 5 or more drinks per day for men or 4 or more drinks per day for women[4]. The choice of PHDD as the primary outcome is based on its endorsement by a recent NIAAA consensus conference[63] and its increasing use in clinical trials[64-66].The 12-week treatment phase will consists of treatment with topiramate or placebo, plus weekly manualized alcohol counseling, added to whatever usual PTSD treatment subjects may be receiving, including medication (exceptions being any other alcohol treatment medications). Subjects will continue to receive usual care for PTSD and other medical and psychiatric disorders from their primary medical and mental health treatment providers. Subjects will meet with research staff weekly to receive medication, counseling and research assessments during the 12 weeks of study treatment. Subjects will also be assessed at the week 16 follow-up visit. The manualized counseling for alcohol use disorders will consist of Medical Management, an NIAAA manual-driven, low-intensity supportive program to promote adherence to the medication regimen and retention.

2) Study Site

The San Francisco VA Medical Center.

3) Characteristics of Study Population

Subjects will be recruited from the San Francisco VA Medical Center and will be men and women, ages 18 through 69, with a diagnosis of PTSD plus a current (past month) harmful or hazardous alcohol use.

4) Inclusion/Exclusion

1) Male and female veterans eligible for VA services.
2) Ages18 to 69 (inclusive)
3) Current DSM-IV diagnosis of PTSD
4) Current (past month) DSM-IV diagnosis of an Alcohol Dependence
5) Level of drinking must meet criteria for “at-risk “ or “heavy” drinking by NIAAA threshold (NIAAA 2007): at least 15 standard drinks per week on average over the 4 weeks prior to study entry for men and at least 8 standard drinks per week on average for women. For Veterans who have been in a controlled drinking environment at study entry, eligibility criteria will be based on meeting "heavy" drinking criteria over the 4 weeks prior to entering the controlled drinking environment.
6) Subjects must express a desire to reduce alcohol consumption with the possible long-term goal of abstinence.
7) Female subjects must have a negative urine pregnancy test and must be either postmenopausal for at least one year, or practicing an effective method of birth control (e.g., surgically sterile, spermicide with barrier, male partner sterilization; or abstinent and agrees to continue abstinence or to use an acceptable method of contraception, as listed above, should sexual activity commence)
8) Subjects must have a Breath Alcohol Concentration (BAC) of 0.00% when signing informed consent.

b) Exclusion Criteria

1) Psychotic disorders, bipolar disorder, dementia, or other psychiatric disorders judged to be unstable.
2) Subjects known to have clinically significant unstable medical conditions, including but not limited to:
   -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 $\leq$ 60 mL/min
   -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
3) History of glaucoma.
4) History of kidney stones.
5) Concurrent participation in another treatment study.

6) Female patients who are pregnant or lactating.
7) Current Topiramate use or use within the past 4 weeks.
8) Current medications for alcohol dependence (disulfiram, naltrexone, or acamprosate) or use in the past week.
9) Needing acute medical detoxification from alcohol based on a score of 12 or more on the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-AD);
10) Subjects who are legally mandated to participate in an alcohol treatment program.
11) Subjects who have had a suicide attempt in the past 6 months or suicidal ideation, with intent, in the 30 days prior to enrollment.
12) Subjects who have previously been treated with topiramate for any reason and discontinued treatment due to an adverse event or due to a hypersensitivity reaction to topiramate,
13) Subjects who in the opinion of the investigator should not be enrolled in the study because of the precautions, warnings or contraindications outlined in the topiramate package insert.

5) Sources of Materials

Research data will be collected from subjects in the form of interviews and questionnaires, subject-completed forms, physical examination, blood and urine samples, and information obtained from the SF VAMC medical record.

6) Potential Risks

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

a) RISKS OF TOPIRAMATE

(1) The most common adverse events:

(a) In the clinical trial of topiramate monotherapy for epilepsy.

At a dose of 400 mg/day the most commonly reported (rate at least 2%) adverse events associated with topiramate include: paresthesias, weight decrease, somnolence, anorexia, dizziness, and difficulty with memory. Other side effects observed in some clinical trials include weight decrease, difficulty concentrating, nervousness, slow thinking, change in sense of taste, abnormal vision, confusion, and language problems. (US Food and Drug Administration 2009).

(b) In the multicenter trial of topiramate in alcohol dependence (Johnson et al. 2007) with topiramate doses of 300 mg/day, adverse events that were reported to occur in 10% or more of participants and that were more frequent in the topiramate vs placebo group were paresthesia (51% vs 11%), taste perversion (23% vs 5%), fatigue (22% vs 18%), anorexia (20% vs 7%), difficulty with concentration and attention (15% vs 3%), nervousness (14% vs 8%), difficulty with memory (13% vs 7%), diarrhea (12% vs 9%), dizziness (12% vs 5%), pruritus (10% vs 1%).

(2) Adverse events (AEs) leading to discontinuation

(a) In the clinical trial of topiramate monotherapy for epilepsy.

In the clinical trial of topiramate monotherapy for epilepsy) at a dose of 400 mg/day: approximately 21% of subjects discontinued due to adverse events (US Food and Drug Administration 2009).

(b) In the multicenter trial of topiramate in alcohol dependence (Johnson et al. 2007) with topiramate doses of 300 mg/day, the attrition rates due to adverse events were 18.6%for the topiramate group and 4.3% for the placebo group.

(3) FDA Warnings appearing in the Package Insert (US Food and Drug Administration 2009)

(a) Suicidality Associated with Anticonvulsants:

An FDA Alert, updated 12/16/2008, (US Food and Drug Administration 2008) listed topiramate as one of 11 antiepileptic or anticonvulsant drugs associated with: "…reports of suicidality (suicidal behavior or ideation [thoughts])…FDA is requiring … that all manufacturers of drugs in this class include a Warning in their labeling.... FDA's pooled analyses of 199 clinical trials of eleven antiepileptic drugs … showed that patients who received one of the antiepileptic drugs had almost twice the risk of suicidal behavior or ideation (0.43%) compared to patients who received placebo (0.24%). This … represents the occurrence of approximately one additional case of suicidal thinking or behavior for every 530 patients treated with an antiepileptic drug….The increased risk was observed as early as one week after starting treatment and throughout the observed duration of treatment. The increased risk of suicidal thoughts or behavior was generally consistent among the eleven drugs with varying mechanisms of action and across a range of indications. This observation suggests that the risk applies to all antiepileptic drugs used for any indication…."

(b) Metabolic Acidosis

"Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate … in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase….Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults … Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may be additive to the bicarbonate lowering effects of topiramate…"(US Food and Drug Administration 2009)

(c) Acute Myopia and Secondary Angle Closure Glaucoma

"A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX®. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure…. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating TOPAMAX® therapy. …. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible…. Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss. "(US Food and Drug Administration 2009)

(d) Oligohidrosis and Hyperthermia

"Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with TOPAMAX® use. …Some of the cases were reported after exposure to elevated environmental temperatures. The majority of the reports have been in children. ... (US Food and Drug Administration 2009)

(e) Withdrawal of AEDs

"Antiepileptic drugs, including TOPAMAX®, should be withdrawn gradually to minimize the potential of increased seizure frequency. " (US Food and Drug Administration 2009)

(f) Cognitive/Neuropsychiatric Adverse Events

"Cognitive-related dysfunction (e.g. confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); The majority of cognitive-related adverse events were mild to moderate in severity... Rapid titration rate and higher initial dose were associated with higher incidences of these events. Many of these events contributed to withdrawal from treatment….In the monotherapy epilepsy controlled trial, the proportion of patients who experienced one or more cognitive-related adverse events was 19% for TOPAMAX® 50 mg/day and 26% for 400 mg/day. …In the 6-month migraine prophylaxis controlled trials using a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse events was 19% for TOPAMAX® 50 mg/day, 22% for 100 mg/day, 28% for 200 mg/day, and 10% for placebo. These dose-related adverse reactions typically began in the titration phase and often persisted into the maintenance phase, but infrequently began in the maintenance phase. … (US Food and Drug Administration 2009)

(g) Kidney Stones

"A total of 32/2,086 (1.5%) of adults exposed to topiramate during its adjunctive epilepsy therapy development reported the occurrence of kidney stones, an incidence about 2-4 times greater than expected in a similar, untreated population. … As in the general population, the incidence of stone formation among topiramate treated patients was higher in men. …An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors… promote stone formation by reducing urinary citrate excretion and by increasing urinary pH." (US Food and Drug Administration 2009)

(h) Other Rare Adverse Effects

"These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, maculopathy, pancreatitis, pemphigus, and renal tubular acidosis." (US Food and Drug Administration 2009)

(i) Contraindicated Medications

Subject will not be allowed to take the following medications because of their possibly harmful interactions with the study medication:

Alcohol Treatment Medications

- acamprosate (Campral®)
- disulfiram (Antabuse®)
- naltrexone (both oral and injectable for extended release) (Revia®, Depade®, Vivitrol®)

Topiramate

b) BLOOD DRAWING (VENIPUNCTURE) RISKS

Participation in the study requires subjects to have their blood drawn 3 different times over the course of 16 weeks. Having blood drawn may cause pain (common), fainting/passing out (not very often), a bruise where the needle goes in (not very often), and infection at the same place (rare).

c) REPRODUCTIVE/PREGNANCY RISKS

Topiramate is classified as Pregnancy Category C. Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. (US Food and Drug Administration 2009) Women participants should not become pregnant while in this study because the effects of topiramate on a fetus are unknown.

d) RISK TO PRIVACY/CONFIDENTIALITY

Participation in the study presents a risk to the subject of loss of privacy and confidentiality regarding research material, particularly with respect to potentially embarrassing or harmful personal health information, particularly related to mental health and alcohol and substance use. This includes detailed and sensitive information regarding alcohol and drug use, and psychiatric symptoms. For example, urine drug testing will be conducted. Potential release of information regarding drug use, in particular, could have serious implications if made known, for example legal ramifications, jeopardizing insurability or employability.

In order to ensure the safety of the subject and others, information may be shared between research staff and the clinical team only under the following circumstances: 1) If in the judgment of the study physician, the subject has a psychiatric or medical condition that requires urgent attention to protect the safety of the subject or others; and 2) If a subject has missed several study appointments, and research staff needs to verify the subject's whereabouts and/or verify the subject's safety. These above circumstances will be clearly outlined in the informed consent form, and be discussed and clarified with prospective subjects at the start of the study.

e) EFFECTS OF TOPIRAMATE ON OTHER MEDICATIONS

Topiramate may interact with other medications, potentially increasing or decreasing their effectiveness.

f) RANDOMIZATION RISKS
Subjects will be assigned to a treatment program by change, and the treatment received may prove to be less effective or to have more side effects than other available treatments.

g) RISK OF RELAPSE TO ALCOHOL USE
Subjects may face the risk of relapse to using alcohol. This risk may be greater if they are assigned to receive placebo as compared to topiramate, although the exact nature of this risk is unknown.

h) RISK OF CESSATION OF CURRENT ALCOHOL ABUSE MEDICATION
Subjects may face the risk of relapse to using alcohol if they stop their current alcohol abuse medication to enroll in this study. This risk may be greater if they are assigned to receive placebo as compared to topiramate, although the exact nature of this risk is unknown.

i) RISK OF DISTRESS/FATIGUE DUE TO PSYCHIATRIC AND NEUROCOGNITIVE ASSESSMENTS
Participants may face to the risk related to answering questions about their medical/psychiatric history, reporting of drug use, and taking part in neurocognitive assessment may include fatigue and distress

i) UNKNOWN RISKS
Subjects may experience side effects that are unknown at this time.
You may experience side effects that we do not know about yet. You should call the study doctor or research staff if you have any symptoms or reactions. The researchers will let you know if they learn anything that might make you change your mind about participating in the study. For more information about risks and side effects, ask the study doctor.

b. Adequacy of Protection Against Risks

1) Informed Consent
Subjects will be educated of the risks attendant to study participation through the informed consent process. See Section D.3.c for description of the informed consent process. See the Informed Consent Form for this study attached to the UCSF CHR application.

2) Protection Against Risks

a) RISKS OF TOPIRAMATE
(1) Suicidality Associated with Anticonvulsants:
To protect against this risk, we will do the following:
- We will follow the guideline suggested by the FDA "…All patients who are currently taking or starting on any antiepileptic drug for any indication should be monitored for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts or behavior or depression." (US Food and Drug Administration 2008).
- Steps taken to follow this guideline are: exclusion of any subject from participation if they have had active suicidal ideation in the 6 months prior to enrollment; weekly interview using the detailed Suicide Risk Assessment Form from the SF VA Medical Center; checking for depression at baseline using the Beck depression inventory; and frequent contacts, as needed, with the subjects mental health clinician(s) at the SF VAMC.
- If active suicidal ideation emerges during study treatment, the subject will be withdrawn from the study, topiramate or placebo will be tapered off over a period of one week, and the study physician will collaborate with the clinical mental health provider to put together a treatment plan that adequately addresses the suicidal thoughts or behavior.
- We have added the following text to the informed consent form: "Like other antiepileptic drugs, TOPAMAX may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Call a healthcare

provider right away if you have any of these symptoms, especially if they are new, worse or worry you: thoughts about suicide or dying, attempts to commit suicide, new or worse depression, new or worse anxiety, feeling agitated or restless, panic attacks, trouble sleeping (insomnia), new or worse irritability, acting aggressive, being angry, or violent, acting on dangerous impulses, an extreme increase in activity and talking (mania), other unusual changes in behavior or mood. Do not stop TOPAMAX without first talking to a healthcare provider. Stopping TOPAMAX suddenly can cause serious problems. Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes. Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. Keep all follow-up visits with your study doctor as scheduled. Call your study doctor, as needed, between visits as needed, especially if you are worried about symptoms. Some patients have had suicidal thoughts or actions. If you feel a change in your mood or if you feel depressed or feel you may harm yourself, please contact your doctor."

(2) Metabolic Acidosis
To protect against this risk, we will do the following:
- We will follow FDA recommendations (US Food and Drug Administration 2009) by measuring baseline and periodic serum bicarbonate every 4 weeks during the treatment phase of the study. We will follow the FDA recommendation: "If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering)." We will consult with the subject's primary care physician regarding any questions concerning possible metabolic acidosis.
- In the informed consent form, subjects will be instructed as follows:
"Metabolic acidosis (decreased bicarbonate in the blood) may be associated with topiramate treatment. Metabolic acidosis can cause symptoms such as tiredness and loss of appetite, or more serious conditions including irregular heartbeat (arrhythmia) or coma. Long-term metabolic acidosis can result in thinning of the bones (osteoporosis) with an increased risk for fractures. In children, this condition may reduce growth rates which may eventually decrease maximum height achieved. Metabolic acidosis may increase the risk for kidney stones."

(3) Acute Myopia and Secondary Angle Closure Glaucoma
To protect against this risk, we will do the following:
- We will screen for glaucoma using the standard method that is currently applied in the clinical care of patients who are being prescribed topiramate for the conditions for which it is already approved: seizures and migraine. This method involves a clinical assessment utilizing patient history and examination of medical records to screen for glaucoma. Current clinical practice applied to the prescribing of topiramate does not include routine examination by an ophthalmologist performing tonometry to directly examine the patient for the presence of glaucoma. In both the warning section and precautions section of the FDA package insert (US Food and Drug Administration 2008) for topiramate (Topamax®) under the heading acute myopia and secondary angle closure glaucoma, there is no requirement or recommendation for ophthalmological examination using tonometry or other methods. Therefore the current standard of care for glaucoma screening relies on patient screening and medical record review. We will follow that standard.
- Adverse event monitoring each week during the course of the study treatment will include a question about symptoms of glaucoma including acute onset of decreased visual acuity and/or ocular pain.
- Following FDA recommendations (US Food and Drug Administration 2009) if ocular symptoms occur, "The primary treatment to reverse symptoms is discontinuation of (topiramate) as rapidly as possible…"
- In the informed consent form, subjects will be instructed as follows:
"A medical condition consisting of sudden worsening of vision and an elevation of fluid pressure in the eyes (acute secondary glaucoma) has been described in patients taking topiramate, usually occurring in the beginning of their treatment. If you have sudden, significant worsening of vision, blurred vision, or eye pain you should contact your doctor immediately."

(4) Oligohidrosis and Hyperthermia
To protect against this risk, we will do the following:
- In the informed consent form, subjects will be instructed as follows:

"Treatment with topiramate may cause decreased sweating (oligohidrosis). Activities such as exercise or exposure to warm temperatures while using topiramate may increase the risk of heat-related side effects, such as heat stroke. Drinking plenty of fluids while using topiramate is recommended."

(5) Withdrawal of anticonvulsants
To protect against this risk, we will do the following:
- Topiramate will be discontinued through a gradual taper over 7 days from 300 mg to zero in week 12 of the study.
- In the informed consent form, subjects will be instructed as follows:
"In patients with and without a history of seizures, it is important to lower the dose of topiramate gradually to reduce the possibility of having seizures when topiramate is stopped. Isolated reports of seizures associated with a rapid decrease of topiramate have occurred in patients with or without seizure disorders. In situations where rapid withdrawal of topiramate is needed, appropriate research monitoring is recommended. You should contact your study doctor immediately if you need to stop taking your topiramate."

(6) Cognitive/Neuropsychiatric Adverse Events
To protect against this risk, we will do the following:
- Inquire about cognitive adverse events at Screening and each week during the study treatment
- Measure cognitive functioning with neuropsychological tests (Trail Making Test Parts A & B and Hopkins Verbal Learning Test) at Screening and at weeks 6 and 12.

(7) Kidney Stones
To protect against this risk, we will do the following:
-Check renal function and serum bicarbonate levels during Screening and every 4 weeks during the treatment phase of the study.
- In the informed consent form, subjects will be instructed as follows:
"Kidney stones have occurred in patients taking topiramate. It is recommended for you to drink between 6 and 8 10-ounce glasses of water per day to reduce the risk of developing kidney stones. This may reduce the risk of kidney stones."

(8) Other rare adverse effects
To protect against these risks, we will do the following:
- Inquire about adverse events at Screening and each week during the study treatment.
- To further promote awareness of the risks involved, the ICF explicitly discusses the potential side effects from taking topiramate and provides subjects with categories of likelihood as follows:

Likely (occurs in greater than 20% or 1 out of every 5 people)
- Numbness and tingling
- Change in sense of taste
- Fatigue
- Headache

Less Likely (occurs in less than or equal to 20% of people)
- Loss of appetite
- Difficulty with concentration and attention
- Nervousness
- Difficulty with memory and language problems
- Diarrhea
- Dizziness
- Itching
- Sleepiness
- Nausea
- Bloating
- Influenza-like symptoms
- Sinus infection

- Muscle pains

Rare but Serious

- Risk of suicide
- Kidney stones
- Metabolic acidosis
- Sudden worsening of vision
- Decreased sweating
- Increased levels of ammonia in blood

The assignment of adverse events to various categories of likelihood was done as follows:
-'Likely' and 'Less Likely' categories data was derived from the largest study that examined a controlled trial of topiramate specifically for alcohol dependence (Johnson et al 2007)
-For 'Rare but Serious' adverse events, information was obtained from the FDA approved package insert for Topamax (topiramate) using adverse event data from controlled trials of topiramate as monotherapy for epilepsy.

(9) Contraindicated Medications
To protect against this risk, we will do the following:
-provide each subject with a wallet-sized card listing the contraindicated medications to facilitate coordination between the study and the subject's primary care physician.
-because all patients are veterans and will be getting their care at the SFVAMC we will monitor all VA clinical medications on a weekly basis via CPRS.

b) BLOOD DRAWING (VENIPUNCTURE) RISKS:
To protect against this risk, we will do the following:
- Professionally trained phlebotomists at the SF VAMC Clinical laboratory will perform all phlebotomy.
- In the informed consent form, subjects are instructed: Having blood drawn may cause pain (common), fainting/passing out (not very often), a bruise where the needle goes in, (not very often), and infection at the same place (rare).

c) REPRODUCTIVE/PREGNANCY RISKS:
To protect against this risk, we will do the following:
- Birth Control/ Pregnancy Assessment will be done at baseline/screening at weeks 4, 8, 12, and 16. Any subject who becomes pregnant during participation in the study will be withdrawn. The results will be recorded on a Birth Control/pregnancy Assessment Form.
- In the informed consent form, subjects are instructed: "You should not become pregnant while on this study because the effects of topiramate on a fetus are unknown. Women of child bearing potential will be asked to use birth control. Acceptable methods include condom AND spermicide, diaphragm AND spermicide, or not having sex. Pregnancy tests will be done monthly throughout your participation in the study to assure that you are not pregnant. If you become pregnant during the study, study treatment will be discontinued and one of your alternative treatment plans may be implemented."
If you are practicing abstinence, you must agree to continue abstinence or use an acceptable method of contraception should sexual activity commence.

d) RISKS TO PRIVACY/CONFIDENTIALITY:
To protect against this risk, we will do the following:

- In the informed consent form, subjects are instructed: "Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. If you do not already have a medical record at the VA Medical Center, San Francisco, one will be created because of your participation in this study."
- *HIPAA regulations will be followed throughout this study.* Several methods will be used to decrease the risk *of loss* of confidentiality to subjects.
    - First, all study forms will be labeled with a unique, identifying code number, and maintained in a locked cabinet. Those that contain the names of participants or other identifying information will be stored in a locked cabinet, separate from other study forms.

- Second, a Certificate of Confidentiality will be obtained from the National Institutes of Health. The function of this document is to protect the principal investigator, and others who have access to the data, from forced disclosure of identifying information during legislative, civil, criminal, or other proceedings, at the local, state, or federal levels.
  Certificate of Confidentiality: A Certificate of Confidentiality from NIH will be acquired for this study to offer protection for the privacy of subjects by protecting identifiable research information from forced disclosure (e.g., through a subpoena or court order). The Certificate of Confidentiality will allow investigators and others with access to research records to refuse to disclose information that could identify subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the Federal, State, or local level. The Certificate of Confidentiality is granted for studies that collect information that, if disclosed, could damage subjects' financial standing, employability, insurability, or reputation, or have other adverse consequences.
- Third, research material will not be shared between the research team and clinical staff - with the exception of information to be shared only to ensure the safety of the subject and others.
- Fourth, no names will be used in any published reports about this study.
- Fifth, data will be collected and maintained using the The Research Database System which will include FDA regulated and non-regulated research studies. The SQL Server Database Engine is the core service for storing, processing, and securing data within the enterprise. Clinical study databases built in sql server also have a data change tracking mechanism, (i.e. audit trail) identifying data changes made by who, when, what changed, and reason for change.

  Electronic data transfer is serviced from a number of external computer applications where data points are generated and stored based on a subject interfacing with a computer application. Implementation of process flow allows the transfer of data between the sql server database and a wide variety of data formats. Additional safeguards include using user authentication to access data on the research server. Different user profiles allow access to specific tables of the sql server database. For example, investigators and their research staff can view and edit data on their own subjects only. Furthermore, unique study identification numbers are used to identify subjects on data forms and transmitting subject names or other identifying information over the internet is not permissible.

  The central system consists of a Dell PowerEdge 2970 mid-range server. Its features include 4GB of RAM and storage allocated to provide 72GB for the operating system and 145GB for the data. There are 2 quad-core processors installed. For fault tolerance and redundancy the server has five 73GB hard drives.

  Operating system installed with Microsoft Windows Server 2003 R2 and SQL Server 2005 database server for processing and housing of clinical data. Microsoft Internet Information Services (IIS) functions as the Web Server for intranet use.

  For backup and disaster recovery of the system and data, a dedicated Dell PowerVault LTO-3 tape drive is employed along with Symantec Backup Exec 2010 R3 as the management software. The LTO-3 system has a capacity (per tape) of 400GB native / 800GB compressed. Backup tape media is encrypted to comply with the Federal Encryption Standard, FIPS-140-2 and stored offsite in a secure vault.

  The server is located in the SFVAMC Information Research Management Systems (IRMS) server room which has 24-hour surveillance, restricted access and resides within the SFVAMC firewall, providing an extra level of security. This room has air-conditioning units, and provides battery backup in case of a power failure. The server is also kept current with virus protection software and security patches. The server components have been validated through a series of installation, qualification and performance protocols.

We anticipate that the above procedures will be highly effective in decreasing the likelihood of loss of

privacy or confidentiality to subjects in the proposed research project.

e) EFFECTS OF TOPIRAMATE ON OTHER MEDICATIONS

To protect against this risk, we will do the following:
-The study physician will review all concomitant medications and determine whether there are potential drug interactions that need to be avoided.
-In the informed consent form, subjects are instructed, "Topiramate may cause a change (increase or decrease) in the effect of some other medications. If you are taking other medications during your participation in this study, your doctor will explain whether topiramate may have an effect and if necessary, may adjust your medication dose."

f) RANDOMIZATION RISKS

To protect against this risk, we will do the following:
-During the informed consent process, key personnel will explain the definition of randomization and its associated risks.
-In the informed consent form, subjects are instructed, "You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than other available treatments."

g) RISK OF RELAPSE TO ALCOHOL USE

To protect against this risk, we will do the following:
-we will closely monitor alcohol use at each weekly visit.
-subjects will be withdrawn from the study if, in the opinion of the PI or the DSMB, there is: sustained clinically significant worsening in the primary outcome measure of alcohol use, suicidal ideation consisting of suicidal intent or plan, unacceptable adverse events judged to be related to study interventions, or any other clinically significant medical, psychiatric, or substance use related poor outcome that makes continued study participation unsafe.

h) RISK OF CESSATION OF CURRENT ALCOHOL ABUSE MEDICATION

To protect against, we will do the following:
-we will closely monitor alcohol use at each weekly visit
-subjects will be withdrawn from the study if, in the opinion of the PI or the DSMB, there is: sustained clinically significant worsening in the primary outcome measure of alcohol use, suicidal ideation consisting of suicidal intent or plan, unacceptable adverse events judged to be related to study interventions, or any other clinically significant medical, psychiatric, or substance use related poor outcome that makes continued study participation unsafe.

i) RISK OF DISTRESS/FATIGUE DUE TO PSYCHIATRIC AND NEUROCOGNITIVE ASSESSMENTS

To protect against this risk, we will do the following:
During the informed consent process, participants are told that they are free to decline to answer any questions or to stop the assessments at any time. Neurocognitive assessments, interview sessions, and computer training will include breaks to help with the potential distress and fatigue. In the event that participants appear to be under undue strain, the session will be immediately discontinued.

i) UNKNOWN RISKS

To protect against this risk, we will do the following:
-During the informed consent process, subjects will be notified about the possibility of unknown risks associated with taking Topiramate.
-At weekly routine visits, subjects will be asked to report any new symptoms or reactions since their last visit.
-Study doctors will inform all study participants if they learn any new side effects of Topiramate. A study doctor will be available 24/7 to field participants' questions and concerns.

c. Adverse Event Reporting

1) Adverse Event Definition

Adverse Events (AEs) will be collected using the definition of the UCSF CHR and International Conference on Harmonization (ICH) for Clinical Safety Data Management (ICH-E2A), according to which an adverse event is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmacological product which does not necessarily have to have a causal relationship with this treatment." An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention (ICH, 1995).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures including laboratory test abnormalities.

2) Serious Adverse Event Definition

Research staff will immediately notify the study physician in the event of a serious adverse event (SAE). In the event of one that is life-threatening or requires hospitalization, the subject's medical status will be monitored and the decision of whether to withdraw the subject from the study will be made on an individual basis by the study physician based on severity and nature of the medical problem. For all adverse reactions that are serious, life-threatening, or require hospitalization, the principal investigator and research coordinator will notify the UCSF CHR and the Federal Drug Administration (FDA) using the standard procedures provided by each agency. Serious adverse events occurring within 30 days following the last dose of study medication will also be reported to HRPO, USAMRAA and CDMRP within 72 hours of the occurrence or report.

d. Subject Withdrawal

Subjects will be withdrawn from the study if:

- in the clinical judgment of the investigator, the subject requires acute detoxification from alcohol,
- in the clinical judgment of the investigator, the subject's clinical condition worsens substantially and it is felt to be in the subject's best interest to obtain alternative treatment including, but not limited to, additional psychotherapy, pharmacotherapy, hospitalization, etc.
- the subject becomes pregnant. Should a subject become pregnant at any time during the study the subject will immediately discontinue study medication. Study medication will not be tapered.

E.2. DATA AND SAFETY MONITORING

a. Plan to Monitor Study Progress and Safety: The Data and Safety Monitoring Plan (DSMP)

The DSMP for this project consists of:
- a Data and Safety Monitoring Board (DSMB)
- a schedule of DSMB meetings to review study data and events
- a list of study data and event items to be reviewed by the DSMB
- procedures for communicating DSMB findings to the CHR, the study sponsor (Department of Defense) and other appropriate entities
- a plan for conducting and reporting interim analysis
- stopping rules
- rules for withdrawing study participants from the study interventions

These elements of the DSMP are described below:

b. The Data and Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) is a group of 3 physicians who are not study investigators and who are experts in the area of PTSD and substance use disorders. The composition of the DSMB is: Steven Lieske, MD, PhD, SFVAMC; William Wolfe, MD, SFVAMC; and Anne Richards, MD, MPH, SFVAMC.

The DSMB will meet biannually to review data reports prepared by the PI regarding the progress of the study and will monitor patient enrollment, retention, outcomes, adverse events, and other issues related to patient safety. The DSMB will make recommendations to the PI as to whether the study should continue or be modified or terminated. The DSMB can consider patient safety or other circumstances as grounds for early termination. Any member of the DSMB can ask for a meeting of the group if he/she feels that it is necessary,

based upon the data.

During the course of the study, reports will be prepared and distributed to the Data and Safety Monitoring Board on a biannual basis. In order for the Data and Safety Monitoring Board to discharge their duties for overseeing the study and the rights of the patients, they will receive analyses of the primary outcome measures and the important secondary measures on a biannual basis. The DSMB will receive reports of serious adverse events (SAEs) within 72 hours of their occurrence.

DSMB Minutes will be prepared by the Study Coordinator within 5 working days after each biannual DSMB meeting.

c. Research Monitor (RM)

Anne Richards, MD, MPH, is an Assistant Clinical Professor at UCSF and Staff Psychiatrist at the SFVAMC. Her clinical and research interests are in the area of traumatic stress. Dr. Richards will serve as Research Monitor. At a minimum, the research monitor: (1) may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research; (2) shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the UCSF CHR can assess the monitor's report; (3) shall have the responsibility to promptly report their observations and findings to the IRB or other designated official. As Research Monitor, Dr. Richards will review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. The medical monitor will comment on the outcomes of the event of problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The Research Monitor will also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the USAMRMC ORP HRPO.

d. Schedule of DSMB Meetings to Review Study Data and Events

The DSMB will meet biannually.

e. List of Study Data and Event Items to be Reviewed by the DSMB

Data reports prepared by the PI regarding the progress of the study will include patient enrollment, retention, analyses of the primary outcome measures (alcohol use) and important secondary outcome measures (depression), adverse events, serious adverse events, and other items related to patient safety.

f. Procedures for Communicating DSMB Findings to the CHR, the Study Sponsor (Department of Defense) and other Appropriate Entities

The PI will communicate DSMB findings in the form of copies of the minutes of each biannual DSMB meeting, within 10 working days following each meeting. Reports will be sent to the CHR, DOD, and SFVAMC Human Research Protection Program (HRPP).

g. Plan for Conducting and Reporting Interim Analyses

Interim analyses will be performed on a biannual basis, prior to each DSMB meeting, and will consist of analyses of the primary outcome of alcohol use, secondary outcome of depression levels, counts and listing of all adverse events, and lists of all SAEs (SAEs will also be reported to the DSMB within 72 hours from the time of their occurrence or from the time study staff became aware of their occurrence).

h. Stopping Rules

The study will be stopped if, in the judgment of the DSMB or the PI, there are sufficient safety concerns that arise during the conduct of the study that would indicate that subjects are being harmed by study interventions. Examples of such safety concerns would be:

- If, after the first 10 subjects (33% of the planned enrollment) have completed their study treatment, the interim analysis reveals that more than 50% (i.e. 6 subjects) have worsened to a clinically significant degree in the primary outcome measure of alcohol use from baseline to study end.

- Other events that pose unacceptable risks to subjects, e.g., multiple SAEs that are judged to be related to study interventions

i. Rules for Withdrawing Study Participants from the Study Interventions

Subjects will be withdrawn from the study if, in the opinion of the DSMB or the PI, there is: sustained clinically significant worsening in the primary outcome measure of alcohol use, suicidal ideation consisting of suicidal intent or plan, unacceptable adverse events judged to be related to study interventions, or any other clinically significant medical, psychiatric, or substance use related poor outcome that makes continued study participation unsafe in the clinical judgment of the PI or DSMB members.

j. Rules for Breaking the Blind

The blind will be broken for an individual in the study if, in the opinion of the PI or DSMB, there is an emergent clinical need to determine whether a subject is receiving topiramate or placebo.

E.3. BENEFITS TO TAKING PART IN THE STUDY

Subjects may benefit from the extra physical examination, laboratory tests, and attention to and treatment of alcohol use disorders.

In the informed consent form, subjects are instructed: "Taking part in this study may or may not make your health better. If you are in this study, you may benefit from the physical examinations, blood tests, and review of your symptoms. You may respond favorably to the treatment and reduce your drinking and PTSD symptoms, but there is no guarantee that this will happen. Others may benefit from the overall conclusions drawn from the results of this study."

REFERENCES

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th ed*. Washington DC: American Psychiatric Publishing.

Anton RF, O'Malley SS, Ciraulo DA, et al. (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *Journal of the American Medical Association*. 295(17), 2003-17.

Anton RF, Moak DH, Latham P. (1995). The obsessive compulsive drinking scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. *Alcoholism: Clinical and Experimental Research,* 19(1), 92-99.

Armitage, S. (1946). *An analysis of certain psychological tests used for the evaluation of brain injury.* American Psychological Association.

Army Individual Test Battery. (1944). *Manual of Directions and Scoring.* Washington, DC: War Department, Adjutant General's Office.

Baker, F., Johnson, M. W., & Bickel, W. K. (2003). Delay discounting in current and never-before cigarette smokers: Similarities and differences across commodity, sign, and magnitude. *Journal of Abnormal Psychology*, 112, 382-392.

Batki, S. L., Dimmock, J. A., Wade, M., Gately, P. W., Cornell, M., Maisto, S. A., et al. (2007). Monitored naltrexone without counseling for alcohol abuse/dependence in schizophrenia-spectrum disorders. *American Journal of Addiction, 16*(4), 253-259.

Beck, A. T., Epstein, N., Brown,G., et al. (1988). An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting Clinical Psychology.* 56, 893-897.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, 4, 561-571.

Beck, A., Steer, R., & Brown, G. (2000). *BDI-FastScreen for medical patients: manual.* San Antonio, TX: Psychological Corporation.

Beckham, J., Crawford, A., & Feldman, M. (1998). Trail making test performance in Vietnam combat veterans with and without posttraumatic stress disorder. *Journal of Traumatic Stress*, 11(4), 811-819.

Berlant J, van Kammen DP. (2002) Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. *J Clin Psychiatry*. 63(1),15-20.

Berlant JL. (2004) Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder. *BMC Psychiatry*, 4,24.

Bickel, W. K., Odum, A. L., & Madden, G. J. (1999). Impulsivity and cigarette smoking: Delay discounting in current, never, and ex-smokers. *Psychopharmacology*, 146, 447-454.

Blake, D. D. et al. (1995) The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress* 8, 75-90.

Bohn MJ, Barton BA, Barron KE: Psychometric properties and validity of the obsessive-compulsive drinking scale. *Alcohol Clin Exp Res* 20(5): 817-823, 1996.

Bowie, C., & Harvey, P. (2006). Administration and interpretation of the Trail Making Test. *Nature Protocols*, 1(5), 2277-2281.

Brady KT, Sonne SC, Roberts JM. (1995) Sertraline treatment of comorbid posttraumatic stress disorder and alcohol dependence. *J Clin Psychiatry*. Nov;56(11):502-5

Brady KT, Sonne S, Anton RF, Randall CL, Back SE, Simpson K. (2005)Sertraline in the treatment of co-occurring alcohol dependence and posttraumatic stress disorder. *Alcohol Clin Exp Res*. (3):395-401.

Brandt, J. (1991). The hopkins verbal learning test: development of a new memory test with six equivalent forms. *The Clinical Neuropsychologist*, 5(2), 125 - 142.

Brown, R., Burgess, E., Sales, S., Whiteley, J., Evans, D., & Miller, I. (1998). Reliability and validity of a smoking timeline follow-back interview. *Psychology of Addictive Behaviors*, 12, 101-112.

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, 28(2), 193-213.

Chilcoat, H.D., Menard, C. (2003). Epidemiologic investigations: Comorbidity of Posttraumatic Stress Disorder and Substance Use Disorder. In Ouimette, P. Brown, P.J. (Eds). *Trauma and Substance Abuse.* American Psychological Association, Washington, DC. 9-28.

Claassen, C., & Adinoff, B. (1999). Alcohol Withdrawal Syndrome: Guidelines for Management. *CNS Drugs*, 12(4), 279.

Coffey, S. F., Gudleski, G. D., Saladin, M. E., & Brady, K. T. (2003). Impulsivity and rapid discounting of delayed hypothetical rewards in cocaine-dependent individuals. *Experimental & Clinical Psychopharmacology,* 11, 18-25.

Cramer JA, Rosenheck R, Kirk G, Krol W. Krystal JH, (2003) for the VA Naltrexone Study Group 425. Medication compliance feedback and monitoring in a clinical trial: Predictors and outcomes. *Value In Health* 2003; 6: 566-573..

Davis L (personal communication: abstract, 2008) Topiramate in the treatment of PTSD: a placebo-controlled study.

Dahlke, F., Lohaus, A., & Gutzmann, H. (1992). Reliability and clinical concepts underlying global judgments in dementia: implications for clinical research. *Psychopharmacology bulletin*, 28(4), 425-432.

Dodgson SJ, Shank RP, Maryanoff BE (2000). Topiramate as an inhibitor of carbonic anhydrase isoenzymes. *Epilepsia*, 41 (4, SUPPL 1): S35-S39.

Ernst, J., Warner, M., Townes, B., Peel, J., & Preston, M. (1987). Age group differences on neuropsychological battery performance in a neuropsychiatric population: An international descriptive study with replications. *Archives of Clinical Neuropsychology*, 2(1), 1.

Feinn R, Tennen H, Kranzler HR. (2003) Psychometric properties of the short index of problems as a measure of recent alcohol-related problems. *Alcohol Clin Exp Res*. Sep;27(9):1436-41.

First, M. B., Gibbon, M., Spitzer, R. L., & Williams, J. B. W. (2001 Revision). *Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version (Patient Edition ed.)*. Washington, D.C.: American Psychiatric Press, Inc.

Flannery, B.A, J. R. V., H. M. Pettinati, (1999). Psychometric Properties of the Penn Alcohol Craving Scale. *Alcoholism: Clinical and Experimental Research*, 23(8), 1289-1295.

Frances K. Del Boca, J. D. (2003). The validity of self-reports of alcohol consumption: state of the science and challenges for research. *Addiction*, 98(S2), 1-12.

Fuller RK, Branchey L, Brightwell DR, et al.(1986). Disulfiram treatment of alcoholism. A Veterans Administration Cooperative Study. *Journal of the American Medical Association*, 256(11): 1449-1455.

Garnett, W. (2000). Clinical pharmacology of topiramate: a review. *Epilepsia*, 41, 61-65.

Gewiss, M. et al., (1991). Acamprosate and diazepam differentially modulate alcohol-induced behavioral and cortical alterations in rates following chronic inhalation of ethanol vapor. *Alcohol Alcohol*, 1991;26:129-137.

Glauser TA. (1999). Topiramate. *Epilepsia*;40 Suppl 5:S71-80.

Gryder DS, Rogawski MA. (2003). Selective antagonism of GluR5 kainate-receptor-mediated synaptic currents by topiramate in rat basolateral amygdala neurons. *J Neurosci*, 23 (18): 7069-7074.

Guy, W. (1976) *ECDEU Assessment Manual for psychopharmacology-Revised* (DHHS Publ. No. ADM 91338). Rockville, MD; USDHHS; pp 218-222.

Harris, BR et al. (2002). Acamprosate inhibits the binding and neurotoxic effects of trans-ACPD, suggesting a novel site of action at metabotropic glutamate receptors. *Alcoholism: Clinical and Experimental Research.* 26(12):1779-93.

Herrero AI, Del Olmo N, Gonzalez-Escalada JR, Solis JM (2002). Two new actions of topiramate: inhibition of depolarizingGABAA -mediated responses and activation of a potassium conductance. *Neuropharmacology*, 42 (2): 210-220.

Hembly, S.E., B.A. Johnson, and S.I. Dworkin (1997). Neurological basis of drug reinforcement, in *Drug Addiction and its Treatment: Nexus of Neuroscience and Behavior*, B.A. Johnson and J.D. Roache, Editors. Lippincott – Raven:Philadelphia. P. 137-170.

Ho, J-D.; Keller, JJ; Tsai, C-Y; Liou, S-W; Chang, C-J; Lin, H-C. (2013) Topiramate use and the risk of glaucoma development: A population-based follow-up study. American Journal of Ophthalmology. 155:336-341.

Hoge, C. W. et al. (2004). Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med*. 351, 13-22.

Hoge, C. W., Auchterlonie, J. L. & Milliken, C. S. (2006). Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. *Journal of the American Medical Association,* 295, 1023-32.

ICH E2A. (1995). Clinical safety data management: definitions and standards for expedited reporting. Federal Register

Intoximeters Incorporated. (Undated) Alco-Sensor IV with memory: features and benefits. Retrieved May 1, 2009, from http://www.intox.com/products/asivm_datasheet.asp?pnid=10
1995. 60:11284–11287.

Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, Javors MA, Ma JZ. (2003) Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet*, 17;361(9370):1677-85.

Johnson BA, Rosenthal N, Capece JA, et al. (2007) Topiramate for treating alcohol dependence: a randomized controlled trial. *Journal of the American Medical Association,* 298(14):1641-51.

Johnson, M. W., & Bickel, W. K. (2002). Within-subject comparison of real and hypothetical money rewards in delay discounting. *Journal of Experimental Analysis of Behavior*, 77, 129-146.

Killgore, W. D., Castro, C. A., & Hoge, C. W. (2010). Preliminary Normative Data for the Evaluation of Risks ScaleBubble Sheet Version (EVAR-B) for Large-Scale Surveys of Returning Combat Veterans. *Military medicine*, *175*(10), 725-731.

King, D., Leskin, G., King, L., & Weathers, F. (1998). Confirmatory factor analysis of the Clinician-Administered PTSD Scale: Evidence for the dimensionality of posttraumatic stress disorder. *Psychological Assessment*, 10(2), 90-96.

Kirby, K., Petry, N., & Bickel, W. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug using controls. *Journal of Experimental Psychology General*, 128, 78-87.

Kraemer HC, Mintz J, Noda S, Tinklenberg J, Yesavage, JA (2006). Caution regarding the use of pilot studies to guide power calculations for study proposals. *Archives of General Psychiatry* ;63:484-489.

Kuslansky, G., Katz, M., Verghese, J., Hall, C. B., Lapuerta, P., LaRuffa, G., et al. (2004). Detecting dementia with the Hopkins Verbal Learning Test and the Mini-Mental State Examination. *Archives of Clinical Neuropsychology*,19(1), 89-104.

Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., et al. (2002). Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *J Exp Psychol Appl*, 8(2), 75-84.

Lejuez, C. W., Aklin, W. M., Zvolensky, M. J., & Pedulla, C. M. (2003). Evaluation of the Balloon Analogue Risk Task (BART) as a predictor of adolescent real-world risk-taking behaviours. *J Adolesc*, 26(4), 475-479.

Lezak, M. (1995). *Neuropsychological assessment*. New York: Oxford University Press.

Lhuintre, J.P., et al. (1985). Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. *Lancet*, 4: 1014-1016.

Lindley SE, Carlson EB, Hill K. (2007) A randomized, double-blind, placebo-controlled trial of augmentation topiramate for chronic combat-related posttraumatic stress disorder. *J Clin Psychopharmacol.* Dec;27(6):677-81.

Littleton, J. (1995). Acamprosate in alcohol dependence: How does it work? *Soc. Stud. Addict. Alcohol and Other Drugs*, 1179-1188.

Madden, G. J., Begotka, A. M., Raiff, B. R., & Kastern, L. L. (2003). Delay discounting of real and hypothetical rewards. *Experimental & Clinical Psychopharmacology*, 11, 139-145.

Mclean, M.J., Bukhari, A.A., Wamil, A.W. (2000). Effects of topiramate on sodium-dependent action-

potential firing by mouse spinal cord neurons in cell culture. *Epilepsia*, 41 (4,1), S21-S24.
McLellan, A. T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., & Argeriou, M. (1992). The Fifth Edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment*, 9(3), 199-213.
McLellan, A. T., Luborsky, L., Woody, G. E., & O'Brien, C. P. (1980). An improved diagnostic evaluation instrument for substance abuse patients: The addiction severity index. *Journal of Nervous & Mental Disease*, 168 (1), 26-33.
McNair, D., Lorr, M., & Droppleman, L. (1971). *Manual profile of mood states*: Educational & Industrial testing service.
NIAAA (2007). *Helping Patients Who Drink too Much*. NIH Publication No, 07-3769, rev. January 2007.
O'Malley S.S., Jaffe A.J., Chang G., Schottenfeld R.S., Meyer R.E., Rounsaville B. (1992). Naltrexone and coping skills therapy for alcohol dependence: a controlled study. *Archives of General Psychiatry*; 49, 881-7.
Peterson, R., & Headen, S. (1984). Profile of mood states. Test critiques, 1, 522-529.
Petrakis IL, Poling J, Levinson C, Nich C, Carroll K, Ralevski E, Rounsaville B. (2006). Naltrexone and disulfiram in patients with alcohol dependence and comorbid post-traumatic stress disorder. *Biol Psychiatry*, 60(7), 777-83.
Putzke, J., Spanagel, R., Tölle, T., & Zieglgänsberger, W. (1996). The anti-craving drug acamprosate reduces c-fos expression in rats undergoing ethanol withdrawal. *European journal of pharmacology, 317*(1), 39- 48.
Rasmusson, D. X., Bylsma, F. W., Brandt, J. (1995). Stability of performance on the Hopkins Verbal Learning Test.*Archives of Clinical Neuropsychology*, 10(1), 21-26.

Reitan, R. (undated). Instructions and procedures for administering the psychological test battery used at the Neuropsychology Laboratory, Indiana University Medical Center: Indianapolis, Unpublished Manuscript.
Reitan, R. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*, 8(271), 76.
Rosenfeld, W. E. (1997). Topiramate: a review of preclinical, pharmacokinetic, and clinical data. *Clinical Therapeutics*,19(6), 1294-1308.
Rosetti, Z.L., Carboni, S. (1995). Ethanol withdrawal is associated with increased extracellular glutamate in the rat striation. *European Journal of Pharmacology*, 283:177-183.
Ruggiero, K., Scotti, J.,Rabalais, A.E. (2003). Psychometric properties of the PTSD checklist - civilian version. *Journal of Traumatic Stress*, 16(5), 495-502.
Rush, A.J., First, M.B., Blacker, D. (2008). *Handbook of Psychiatric Measures* (2nd ed.). Arlington, VA: American Psychiatric Publishing, Inc.
San Francisco VA Medical Center. (2009). Suicide Risk Assessment Worksheet [Internal Diagnostic Document]. SanFrancisco: Christopher Galloway.
Sankoh, .A.J, Huque, M.F., Dubey, S.D. (1997). Some comments on frequently used multiple endpoint adjustments methods in clinical trials. Statistics in Medicine 1997;16:2529-2542.
Sass ,H., Soyka, M., Mann, K., Zieglgansberger, W. (1996). Relapse prevention by acamprosate: results from a placebo-controlled study on alcohol dependence. *Arch Gen Psychiatry*, 53(8), 673-80.
Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R. & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction*, 88, 791-804.
Schuckit, MA, Smith, TL, Tipp, JE.(1997). The self-rating of the effects of alcohol (SRE) form as a retrospective measure of the risk for alcoholism. *Addiction*, 92: 979–988.
Schuckit, MA, Tipp, JE, Smith, TL, Wiesbeck, GA, Kalmijn, J. (1997). The relationship between self-rating of the effects of alcohol and alcohol challenge results in ninety-eight young men. *J. Stud. Alcohol*, 59: 397–404.
Seal KH, Bertenthal D, Maguen S, Gima K, Chu A, Marmar CR. (2008) Getting beyond "Don't ask; don't tell": an evaluation of US Veterans Administration postdeployment mental health screening of veterans returning from Iraq and Afghanistan. *Am J Public Health*, 98(4):714-20.
Sellers, E. M., Sullivan, J. T., Somer, G., & Sykora, K. (1991). Characterization of DSM-III-R criteria for uncomplicated alcohol withdrawal provides an empirical basis for DSM-IV. *Arch Gen Psychiatry*, 48(5), 442-447.
Shum, D., McFarland, K., Bain, J. (1990). Construct validity of eight tests of attention: Comparison of normal

and closed head injured samples. *Clinical Neuropsychologist*, 4(2), 151-162.
Sillanaukee, P. (1996). Laboratory markers of alcohol abuse. *Medical Council on Alcohol*, 31(6), 613-616.
Simpson TL, Saxon AJ, Meredith CW, Malte CA, McBride B, Ferguson LC, Gross CA, Hart KL, Raskind M. (2009) A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. Alcohol Clin Exp Res. Feb;33(2):255-63.
Sobell L.C., Sobell, M. B., Maisto, S.A., & Cooper, A. M. (1985). *Time-line follow-back assessment method*. Washington, D.C.: National Institute on Alcoholism and Alcohol Abuse.
Sobell LC, Sobell MB (1992) Timeline Follow-Back: a technique for assessing self-reported alcohol consumption. *Measuring Alcohol Consumption: Psychosocial and Biological Methods.* Edited by Litten RZ, Allen J. Towota, NJ, Humana Press, pp 41-72.
Spanagel, R. & Zieglegansberger, W. (1997). Anti-craving compounds for ethanol: new pharmacological tools to study addictive processes. *Trends in Pharmacological Sciences*,1997;18:54-58.
Spreen, O., & Strauss, E. (1998). *A compendium of neuropsychological tests: Administration, norms and commentary (2nd ed.)*. New York: Oxford University Press.
Spreen, O., & Benton, A. (1965). Comparative studies of some psychological tests for cerebral damage. *The Journal of Nervous and Mental Disease*, 140(5), 323.
Stuss D, Stethem L, Pelchat G. Three tests of attention and rapid information processing: An extension. *The Clinical Neuropsychologist.* 1988;1:139-152.
Tucker, P., Trautman, R.P., Wyatt, D.B., Thompson, J., Wu, S.C., Capece, J.A., & Rosenthal, N.R. (2007) Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*, 68(2), 201-6.
US Food and Drug Administration (2008) (http://fda.gov/cder/drug/infopage/antiepileptics/default.htm; accessed 4/30/09)
US Food and Drug Administration (2009) Package Insert labeling Revision, approved April 22, 2009. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020505s036,020844s030lbl.pdf accessed 4/30/09)
Ventura, J., Liberman, R., Green, M., Shaner, A., & Mintz, J. (1998). Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). *Psychiatry Research*, 79(2), 163-173.
Volpicelli, J.R., Alterman, A.I., Hayashida, M., O'Brien, C.P. (1992). Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry*, 49, 876-880.
Weathers, F. W. & Litz, B. T. (1994) Psychometric properties of the Clinician-Administered PTSD Scale, CAPS-1. *PTSD Research Quarterly,* 5, 2-6.
Wechsler D (1997) The Wechsler Adult Intelligence Scale. 3rd ed. The Psychological Corporation, San Antonio, TX
White, H.S., Brown, S.D., Woodhead, J.H., Skeen, G.A., & Wolf, H.H. (2000). Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. *Epilepsia*, 41 (4, SUPPL 1), S17-S20.
Whitworth, A., Fischer, F., Lesch, O., Nimmerrichter, A., Oberbauer, H., Platz, T., et al. (1996). Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. *Lancet, 347*(9013), 1438.
Williams, D., Lewis, J., & McBride, A. (2001). A comparison of rating scales for the alcohol-withdrawal syndrome. *Alcohol and Alcoholism*, 36(2), 104-108.
Wojcik, M.H. & Hawthorne, J.S. (2007). Sensitivity of commercial ethyl glucuronide (EtG) testing in screening for alcohol abstinence. *Alcohol & Alcoholism*. 42(4), 317-320.
Wurst, F.M., Skipper, G.E. & Weinmann, W. (2003). Ethyl glucuronide - the direct ethanol metabolite on the threshold from science to routine use. *Addiciton*, 98(Supple. 2), 51-61.
Zhang, X.L., Velumian, A.A., Jones, O.T., Carlen, P.L. (2000). Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. *Epilepsia*, 41 (4, SUPPL 1), S52-S60.