I. Protocol Information

Title: Zonisamide in addition to Enhanced Cognitive Processing Therapy-C (E-CPT-C) for Veterans with PTSD and Comorbid Alcohol Dependence
Proposal number: 102450059
Phase: II
Version/Date of Protocol: 11/24/15

II. Sponsor Information

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

III. Principal Investigator's Information

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IV. Roles and Responsibilities

The P.I. will be responsible for making eligibility/termination decisions, obtaining informed consent, evaluating adverse events, making data entries or corrections, and seeing protected health information (PHI). Provide oversight on all aspects of the research study.

The Study Coordinator will be responsible for study recruitment, collection of the assessments, data management, and regulatory correspondence. Assist in preparing data for presentations and publications. Prepare records for the Data Safety Monitoring Board.

Co-investigators will be responsible for medical coverage, medical supervision and physical examinations. They will also be part of the data analysis, summary reports, interpreting results, preparation of scientific manuscripts.

Study nurses will be responsible for meeting with subjects weekly to follow their response and side effects to the medication. Maintain all appropriate nursing documentation according to the Good Clinical Practice and VA Connecticut Healthcare System Nursing Procedures.

Study clinicians will be responsible for conducting the E-CPT-C therapy.

Laboratory Technician will be responsible for running EtG and urinary cotinine levels and will coordinate about issues related to organizing sample collection.

V. Site Information

All aspects of the study will be conducted at the West Haven VA Hospital. 950 Campbell Avenue. West Haven, CT 06516

VI. Study Information

This study is designed to determine if the drug Zonisamide is more effective than placebo in decreasing alcohol use and PTSD symptoms when used in combination with Enhanced Cognitive Processing Therapy (E-CPT-C) in veterans with Post-Traumatic Stress Disorder (PTSD) and comorbid alcohol dependence.

VII. Study Design

Background

In the general adult population, posttraumatic stress disorder (PTSD) has a lifetime prevalence rate ranging from approximately 5 - 10% (Berlant 2004; Breslau 2001; Kessler et al 1995). It is a serious psychiatric disorder that tends to be chronic with one third of sufferers having symptoms more than ten years after experiencing the traumatic event (Berlant 2004; Iancu et al 2002). The symptom profile for PTSD includes clusters of symptoms that fall into three categories: avoidance, arousal and re-experiencing. Some groups are more likely than the general population to suffer from PTSD, and that includes veterans particularly those who have experienced combat. There has been an increase in the number of veterans served per year, and the rate of those with PTSD is increasing at a greater rate than other mental disorders (Hermes et al 2012). In FY 2011, 604,719 veterans treated in the Veterans Health Administration (VHA) nationally were diagnosed with PSTD. In FY 2010, 485,843 veterans were treated in Mental Health Clinics with the diagnosis of PTSD, representing 42% of those treated in mental health clinics (Hermes et al 2012). This increase in numbers is accompanied by an increase in intensity in treatment utilization.

There is a high rate of comorbidity with alcohol dependence in individuals with PTSD (Jacobsen et al 2001). Among veterans, 11.8% of those returning from the recent conflicts reported alcohol misuse (Milliken et al 2007) and the rates were higher at post deployment than pre deployment. Individuals diagnosed with comorbid PTSD and alcohol dependence tend to be more impaired and have poorer treatment prognosis than those diagnosed with PTSD or alcohol dependence alone. While there are established pharmacotherapies to treat PTSD alone and to treat alcohol dependence alone, there are no medications established to treat the patients who have comorbid disorders.

Given the high priority for the treatment of PTSD, the Veterans Administration and the Department of Defense (DoD) have invested in making access to evidenced based treatments a priority. This includes Cognitive Processing Therapy (CPT), (CPT; (Resick and Schnicke 1992)) which is based on an information processing theory of PTSD and is an integration of psychoeducation, cognitive therapy and imaginal exposure therapy. Currently, CPT is being rolled out nationally in a large dissemination project by the U.S Department of Veterans Affairs (VA) and the DoD as one of the gold standard treatments for PTSD. However, it's use in veterans with comorbid alcohol use disorders and in conjunction with pharmacotherapies for alcohol use disorders is unknown.

Alcohol Dependence:

Limitations of Current Medications to Treat Alcohol Dependence: There are currently four Food and Drug Administration (FDA)-approved medications in current use for the treatment of alcoholism (disulfiram, naltrexone oral and naltrexone intramuscular, and acamprosate). However, all four have clinical limitations. Disulfiram is an aversive agent and has been used clinically in the management of alcohol dependence for over 50 years. Although our group found that disulfiram did improve some outcomes compared to no medication, in terms of alcohol use the only difference was in the consecutive days of abstinence (Petrakis et al 2005). Further, it is not accepted by all patients, and does not treat the comorbid condition. The opioid antagonist naltrexone is not widely accepted and prescribed for the treatment of alcoholism (Mark et al 2003; Petrakis et al 2003; Thomas et al 2003). In the most recent and largest trial to date, the COMBINE trial, naltrexone had only a modest effect on alcohol consumption (Anton et al 2006). The third medication, acamprosate, received FDA approval largely on the basis of 3 large European trials (Food and Drug Administration (FDA) 2004). However, in the COMBINE trial, there was no advantage of acamprosate over placebo (Anton et al 2006). An intramuscular version of naltrexone (Vivitrol) was approved by the FDA in 2006; studies suggest it is effective and well tolerated for treatment seeking alcohol dependent individuals (Garbutt et al 2005). However, as it is given intramuscularly, severe reactions at the site of injection have been reported; it is also prohibitively expensive.

Pharmacologic strategies using medications to treat alcohol use disorders in patients with comorbidity of PTSD and alcohol dependence have also been tried. A study using adjunctive naltrexone or disulfiram or the combination (Petrakis et al 2005) suggested that these agents confer a modest advantage over no medication to treat alcoholism in individuals with PTSD. In a study of antidepressants for veterans with PTSD, naltrexone did not add additional benefit to antidepressant treatment for alcohol consumption (Petrakis et al 2012). The medications to treat alcoholism have not been embraced by clinicians or patients and are not used widely (Harris et al 2010; Petrakis et al 2003); disulfiram in particular has limited patient and clinician acceptability.

Clearly, the development of new medications to treat alcohol dependence in veterans with PTSD is of high clinical importance and a high priority for the Departments of Defense and the Veterans Administration. Medications to treat alcohol dependence must be compatible within the context of the health care system where veterans are treated. Ideally, medications to treat alcohol dependence will also attenuate symptoms of PTSD <u>or</u> be able to be delivered in conjunction with other treatments for PTSD, such as the Evidence Based Therapies (EBT).

Post Traumatic Stress Disorder:

*Zonisamide and other anticonvulsants in treatment for PTSD***:** The use of anticonvulsants represents a novel approach to treatment that may target symptoms of both alcohol dependence and PTSD. Chronic stress, as that experienced by subjects diagnosed with PTSD, can alter the balance between excitatory and inhibitory processes regulated by GABA and glutamate. Heightened glutamate activation unregulated by low levels of GABA can lead to toxicity and even cell death (Armanini, Hutchins et al. 1990; Thomas 1995). It has been hypothesized that such alterations can lead to frequent reexperiencing and arousal symptoms in individuals suffering from PTSD. Using animal models, studies show topiramate (Khan and Liberzon 2004) and lamotragine (Mirza, Bright et al. 2005) attenuate anxiety responses in rats.

A small clinical literature exists as well. Topiramate has been successfully used as an add-on agent to treat veterans with refractory symptoms of PTSD (Akuchekian and Amanat 2004), and as a mono therapy to treat combat (Alderman, McCarthy et al. 2009), and non-combat symptoms of PTSD (Tucker, Masters et al. 2004; Andrus and Gilbert 2010). A meta-analysis of studies using valproate in PTSD (Adamou, Puchalska et al. 2007) also suggests that anticonvulsants can be used successfully to treat PTSD. *While zonisamide has not been formally tested for PTSD, a pilot study that used zonisamide as an adjunct to anxiolotic therapy in patients with marked anxiety provided preliminary evidence for zonisamide's efficacy in reducing anxiety symptoms. Given zonisamide's similarity to topiramate in terms of its neurobiology and efficacy in other clinical syndromes and potential as a mood stabilizing and anxiolytic, zonisamide is worth exploring as a potential pharmacotherapy for symptoms of PTSD.*

Enhanced Cognitive Processing Therapy E-(CPT)-C: Cognitive Processing Therapy (CPT; (Resick and Schnicke 1992)) was developed for the treatment of PTSD for rape victims. It is based on an information processing theory of PTSD and is an integration of psychoeducation, cognitive therapy and imaginal exposure therapy. CPT has shown to be effective in reducing symptoms of PTSD in both individual and group therapy formats (Resick, Nishith et al. 2002) and improvements in PTSD symptoms appear to be sustained over time (Chard 2005). Although CPT was originally developed and tailored for sexual assault victims, it has been successfully used among military veterans (Monson, Schnurr et al. 2006), incarcerated adolescents (Ahrens and Rexford 2002), and refugees (Schulz, Resick et al. 2006). Currently, CPT is being rolled out nationally in a large dissemination project by the U.S Department of Veterans Affairs and the U.S. Department of Defense as one of the gold standard treatments for PTSD.

Traditional administration of CPT includes two imaginal exposure therapy sessions that utilize written accounts. In order to facilitate emotional processing of traumatic experiences, patients are asked to write about their traumatic experiences, and to read them out loud. Through the use of Socratic questioning, therapists challenge patients' erroneous conclusions about the events. In the course of conducting a dismantling study, Resick et al. (Resick, Galovski et al. 2008), developed CPT-C, the cognitive therapy only version of CPT. In CPT-C, the two sessions devoted to the writing and sharing of trauma accounts are eliminated and there is greater focus on Socratic questioning. Results from this dismantling study demonstrated that all three treatments (i.e., standard CPT, CPT-C, and imaginal exposure through written accounts) were effective in reducing symptoms of PTSD in the long run. However, CPT-C was associated with the quickest reduction of depression and PTSD symptoms. Additionally, a significant reduction in PTSD symptoms was observed for patients in the CPT-C condition at week 2. This was not the case for patients in the standard CPT or the imaginal exposure treatment groups (Resick, Galovski et al. 2008).

Given the demonstrated efficacy of CPT-C for treating PTSD symptoms, and coping skills training for the treatment of alcohol dependence, it is fitting to develop a standardized treatment manual that integrates these treatment approaches. Our group has been developing an "Enhanced CPT-C (E-CPT-C)" a new standardized 12-week therapy that integrates CPT-C (cognitive therapy only version of CPT) with coping skills training for alcohol dependence that can more effectively and simultaneously treat PTSD and alcohol dependence. In piloting this new treatment, our group has developed a manual for its use and is rigorously testing its efficacy with standardized scales evaluating symptoms for PTSD (Clinician Administered PTSD

Symptom Scale-CAPS) and alcohol consumption using the Timeline Follow-back Method (TLFB), as well as mood ratings and quality of life data. The study has now enrolled 9 subjects to participate in treatment with this modified therapy. Our experience has shown that E-CPT-C can be used safely and effectively in veterans with PTSD and comorbid alcohol dependence. Findings from our preliminary data (please see preliminary data section with n=5 completers) has shown that E-CPT-C is effective in reducing symptoms of PTSD (significant decrease in CAPS from 60.5, sd=9.6 at baseline to 20.3, sd=19.9 at post treatment; p=0.03). Unfortunately, its efficacy in reducing alcohol consumption is less robust. However we have reported on its effective use in combination with an established pharmacotherapy for alcohol dependence, disulfiram; E-CPT-C was effective in treating symptoms of PTSD, and alcohol use decreased after initiation of disulfiram (see pilot data).
Based on those findings we propose to conduct a 12-week pilot study for the feasibility and efficacy of combining zonisamide (400mg) as an adjunct to E-CPT-C for veterans with PTSD and comorbid alcohol dependence. We propose to compare zonisamide to placebo in conjunction with E-CPT-C to evaluate efficacy, safety, tolerability and side effects - including cognitive effects.

Significance:

Veterans, especially those with combat experience, are at increased risk for developing PTSD. Rates of PTSD among previously deployed Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) veterans range from 14% to 21%. Alcohol use disorders (AUDs) are the most common comorbid conditions among veterans with PTSD, and as many as 75% of combat veterans with lifetime PTSD also meet criteria for AUDs. Evidence suggests that the emerging pattern of PTSD and AUD comorbidity among OIF/OEF combat veterans is similar to that of combat veterans from previous wars. Veterans diagnosed with comorbid PTSD and alcohol dependence tend to be more impaired and have poorer treatment prognosis than those diagnosed with PTSD or alcohol dependence alone.

The study we are proposing has the potential to influence the way treatment of PTSD and alcohol dependence is delivered across the VA Healthcare Administration (VHA) and the Department of Defense. The population we are going to study are veterans that have served in the military and may have participated in past or current military conflicts. All participants will have current Diagnostic and Statistical Manual of Mental Disorder, 4th Edition (DSM-IV) diagnoses of PTSD and alcohol dependence, two of the most common diagnoses among veterans particularly those who have experienced combat.

Currently Cognitive Processing Therapy (CPT) and CPT-C (CPT without imaginal exposure) are being rolled out nationally in a large dissemination project by the Veterans Health Administration (VHA) and the Department of Defense (DoD) as one of two gold standards for the treatment of PTSD. Unfortunately, neither CPT nor CPT-C address the needs of patients with comorbid alcohol dependence. Our study will further test a newly developed enhanced CPT-C (E-CPT-C) for veterans with PTSD and comorbid alcohol dependence. The study will test E-CPT-C in combination with a new pharmacotherapy for veterans with PTSD and alcohol dependence. Zonisamide is a promising new pharmacotherapy for alcoholism. If effective, it has the potential to be prescribed as a first line medication for alcoholism for veterans.

Overview:

This is a randomized, controlled trial with 100 veterans diagnosed with PTSD and comorbid alcohol dependence. Veterans will be randomized to receive either zonisamide (400 mg) or placebo for 12 weeks in a double blind fashion. Randomization will be done using 3:1 ratio and will be performed by our research pharmacy using a random assignment in blocks of 4- 3 will be assigned to active medication and 1 to placebo.. Medication will be titrated over a 6 week titration phase followed by a 6 week treatment phase. All veterans will receive E-CPT-C therapy for the 12 weeks of treatment; E-CPT-C will be provided by trained and qualified clinicians with extensive experience providing E-CPT-C. Veterans will be recruited primarily through advertisement, but also through the clinical facilities at the VA and from other collaborators.

Experimental subjects:

Fifty veterans aged 21- 65 years old, with a current Diagnostic and Statistical Manual-IV, TR (DSM-IV) diagnosis of PTSD, assessed by the Structured Clinical Interview for DSM Disorders (SCID) & Clinician Administered PTSD Scale for DSM-IV (CAPS), and alcohol dependence (assessed using Structured Clinical Interview for DSM-IV) will be enrolled.

Study Procedures:

Overview: After signing informed consent, participants will undergo an initial assessments and screening. The screening will consist of careful psychiatric and medical evaluation that will also include screening for a veteran's potential to develop alcohol withdrawal. Those veterans who need treatment for alcohol withdrawal will be referred to our detoxification clinic as a first line of treatment. Initial assessments will include a careful diagnostic evaluation completed by highly trained and experienced research personnel, as well as collection of baseline assessments of alcohol use, PTSD symptoms and other characteristics. Veterans will be randomized to zonisamide 400mg or placebo for 12 weeks. The dose and titration schedule for zonisamide was selected based on data from clinical trials and is consistent with the recommended dosing schedules. All veterans will also be enrolled in E-CPT-C therapy. Assessments will occur weekly. At each visit veterans will have an interview with a member of theresearch staff whom is not providing the E-CPT-C training, receive a supply of medication, and complete self-report measures. Veterans will be compensated for their participation using a schedule outlined below. There will be one follow up session 3 months after completion of treatment.

Initial Assessments/Screening: In order to qualify for participation, veterans will complete the following: (I) Diagnostic interview with the Structured Clinical Interview for DSM Disorders (*SCID I)*, a comprehensive psychiatric interview schedule designed to assess psychiatric disorders in adults (First et al 1996). The SCID interview schedule covers the major Axis I psychiatric disorders defined in DSM-IV. The SCID permits comprehensive assessment of substance use as well as comorbid psychiatric disorders. (2) Drinking patterns will be assessed using The TLFB method (Sobell and Sobell 1992). This will allow documentation of the degree and frequency of daily alcohol consumption and smoking pattern. (3) PTSD symptom will be assessed using the *Clinician Administered PTSD Assessment (CAPS*), and (4) Veterans will have a medical history and physical examination by one of the investigators, blood tests (including SMAC-20, serum gamma-glutamyl transferase (γ-GGT), CBC with differential, thyroid function tests,and TSH), urinalysis, urine toxicology, and an electrocardiogram (EKG). It is anticipated, however, that

mild to moderate elevations in liver function tests will be common in alcohol dependent subjects. Veterans with LFT abnormalities that do not exceed 3 times normal values will be included.

Study Treatments:
Medication Treatment*:* Zonisamide, (target 400 mg) will be titrated upward over 6 weeks. Dosing will be given once daily and veterans on placebo will be given identical number, color and consistency of capsules as those on active medication. Below is the proposed dosing schedule, although we will make adjustments if side effects occur:

Zonisamide 400mg/day

Week 1:	Days 1-7	ZON 100mg, +	= TOTAL 100mg
Week 2:	Days 1-7	ZON 200mg, +	= TOTAL 200mg
Week 3:	Days 1-7	ZON 200mg, +	= TOTAL 200 mg
Week 4:	Days 1-7	ZON 300mg, +	= TOTAL 300 mg
Week 5:	Days 1-7	ZON 300mg, +	= TOTAL 300 mg
Week 6:	Days 1-7	ZON 400mg, +	= TOTAL 400 mg
Week 7-12:	Days 1-42	ZON 400mg, +	= TOTAL 400 mg
Week 13-14:	TAPER by 100 mg every 3 days for a total of 2 weeks.		

Medication Adherence: We employ a number of strategies to insure maximum compliance with the medication regiment. Before starting medication each participant meets with the nurse to go over medication regiment, possible side effects and importance of compliance with study medication. All medications will be dispensed in blister packs, clearly labeled with date and time (am or pm) for administration. Within the first week, each participant will receive an additional courtesy phone call from the nurse inquiring about any problems or issues relevant to taking the study medication. Participants will be given the option to come in within the first week and discuss with the nurse any issues relating to medication. Before each visit each participant will receive a reminder phone call about his appointment and is also reminded to return the blister pack with the study medication regardless of whether any medication is left over. At the beginning of each study visit the left over medication will be counted and the participant will be prompted to report any doubling of dose or missing days of study medication. As a final measure of compliance participants are told that a medication blood levels may be drawn.

Justification for zonisamide dose: Zonisamide is approved for the adjunctive treatment of partial seizures in adults with epilepsy. Zonisamide has shown efficacy or potential efficacy in treating bipolar depression or subtypes of bipolar disorder (Anand et al 2005; Baldassano et al 2004; Ghaemi et al 2006; Kanba et al 1994; McElroy et al 2005; McIntyre et al 2002), and demonstrated efficacy in weight reduction in overweight individuals, and potential efficacy in the treatment of binge eating (Gadde et al 2003; Li et al 2005; McElroy et al 2004). It has been used as a potential treatment for alcohol use in several clinical trials, including the pilot study conducted by our group. The usual dose of zonisamide is 200-400 mg, although the dose used in our pilot study was 500 mg. Other studies suggest its efficacy at 400 mg, and a large ongoing clinical trial (clinicaltrials.gov) is using 400 mg, suggesting this dose may be effective. Further, given that this study is conducted in veterans with comorbidity, and the goal is to allow subjects to also participate in E-CPT-C therapy, we have chosen a dose of 400mg.

Pharmacy Procedures: Veterans will start study medication on the day of randomization. The authorized prescribers of zonisamide for the study are Ismene Petrakis, M.D., Louis Trevisan, M.D., Albert Arias, M.D., Kevin Severino, MD and Ellen Edens, M.D. The research pharmacy will dispense the medications and will take back any medications that are not used, keeping a record of used and unused medications. In addition to that we will record at each visit that the medication was dispensed, the number of pills, and if any medications were missed during the previous week. The study nurse will administer the first dose and veterans will be asked to stay in the research office for approximately 1 hour after the dose is administered. The zonisamide will be started at a low dose (see schedule above) and titrated upward based on the outlined schedule. The target dose for the zonisamide will be 400mg/day. Veterans will meet with the study nurse every visit to discuss any side effects of the medications, and will do study assessments with the research personnel. If veterans experience side effects that cannot be managed by adjustments in the timing of the medication (i.e. taking at bedtime, etc.), veterans may have their medication titration either held or the medication dose may be decreased. The study psychiatrist (who is blinded to the condition, but may request a dose decrease to the next lowest dose) and the research pharmacist (who is not blinded, but who has no contact with the veteran) will do this. The psychiatrist will contact the pharmacist and request a decrease in dose. In case of an emergency, the blind will be broken and appropriate medical care initiated. Since this is a pilot study, the proposed dosing schedule will be evaluated and may be modified depending on the findings from the pilot study.

CPT: Cognitive Processing Therapy (CPT) is a manualized 12-session therapy that combines cognitive and exposure-based therapies and has been designed for patients with PTSD (Pettinati et al 2000). The stated goal of CPT is "to assist the client in refraining from assimilating (distorting the event to fit prior beliefs) and in accommodating schemas to the new information without over-accommodating" (p. 17; Resick & Schnicke, 1996 (Resick and Schnicke 1996)). CPT uses Socratic questioning targeting distorted cognitions such as self-blame, hindsight bias, and other guilt cognitions. CPT-C is focused on the cognitive components of the therapy without exposure. CPT-C was chosen over CPT for the following reasons: 1) the exposure component of CPT may place participants at greater risk of increased drinking to cope with increased PTSD symptoms, 2) CPT-C appears to have a higher retention rate and more rapid decline in PTSD and depressive symptoms.

E-CPT-C: Based on previous work by our research group, CPT-C (Resick et al 2007) will be *enhanced* in the following ways to address alcohol use:

1) Additional psychoeducation about alcohol use as an avoidance of PTSD symptoms and the importance of not avoiding thoughts and feelings.
2) Clinician administered weekly breathalyzer to measure blood alcohol level (BAL).
3) Integration of alcohol use as an avoidance of PTSD symptoms (e.g., A-B-C, challenging beliefs, patterns of problematic thinking worksheets to be completed on alcohol use) and role of drinking throughout treatment.
4) Use and collection of daily diaries of alcohol use.

All of the therapy will be provided by doctoral level psychologists. These psychologists will be trained in conventional CPT-C through the VA rollout initiative, then will use the E-CPT-C described in our manual. The two psychologists who have been instrumental in the development of E-CPT-C will either conduct the therapy or train other members of our team. Independent assessment of veterans' PTSD and alcohol dependence symptoms will be obtained by another member of the research team; this is being done to ensure that we obtain unbiased ratings of PTSD and alcohol dependence symptoms.

Justification for use of E-CPT-C: This intervention will be used for the following reasons: (1) CPT-C with modification is able to provide an integrative intervention throughout treatment; (2) both CPT and CPT-C have been effectively adapted for use in veterans, and are part of a national dissemination project; and (3) most importantly, the efficacy of CPT has been established in four separate randomized controlled trials.

Confirmation of self reported alcohol use: Ethyl glucuronide (EtG) (B,T,F) provides a sensitive and reliable biomarker of recent alcohol consumption and is detectable in urine for up to three days after drinking depending upon the amount consumed (Jatlow and O'Malley 2010; Sarkola et al 2003; Wurst et al 2006; Wurst et al 2004). Comparison of urine EtG levels during treatment at weeks 4, 8, 12 with baseline values will provide a quantitative approximation of relative changes in alcohol exposure. For other time-points, EtG concentrations will be assayed only if a veteran self-reports abstinence or no heavy drinking and will be used in secondary analyses of composite outcomes based on self-report confirmed by EtG. Heavy exposure to non-beverage sources of ethanol such as some mouthwashes and hand washes, particularly the latter, can confound interpretation of urinary EtG assays and will be monitored. Normalization to urine creatinine concentration will correct for extremes in urinary dilution.

Research Objectives:

Specific Primary Aim # 1: To determine if zonisamide is more effective than placebo in decreasing alcohol use when used in combination with E-CPT-C in veterans with PTSD and comorbid alcohol dependence.

1a. *We hypothesize that zonisamide will be more effective than placebo when used in combination of E-CPT-C, in reducing heavy drinking days measured by the Timeline Follow-back Method (TLFB).*

1b. We hypothesize that zonisamide will be more effective than placebo when used in combination of E-CPT-C, in reducing drinks per week as measured by the Timeline Follow-back Method (TLFB).

1c. We hypothesize that zonisamide will be more effective than placebo when used in combination of E-CPT-C, in reducing craving for alcohol using the Obsessive Compulsive Drinking Scale (OCDS).

Exploratory Aim #1: To determine if the combination of zonisamide with E-CPT-C is more effective than placebo in reducing symptoms of PTSD. PTSD symptoms will be assessed weekly using the PCL, and biweekly using the CAPS.

Exploratory Aim #2: To determine if zonisamide can be prescribed safely and effectively in veterans who are receiving E-CPT-C. Treatment retention as well as side effects will be monitored.

VIII. Inclusion/Exclusion Criteria

Inclusion Criteria:

1) Males and females between the ages of 21-65 years old.
2) Current alcohol dependence, as determined by a structured clinical interview (Structured Clinical Interview for DSM-IV Axis I Disorders) (SCID) (First et al 1996).
3) Current PTSD as determined by a structured clinical interview (SCID) (First et al 1996).
4) Veterans with current alcohol dependence, with at least one recent episode of heavy drinking (>4 standard drinks/sessions for men and >3 standard drinks/sessions for women) over the past 14 days.
5) Medically and neurologically healthy on the basis of history, physical examination, EKG, screening laboratories (CBC w/ differential, TSH, Free-T4, ASAT, ALAT, GGT, BUN, creatinine, calcium, phosphorous, magnesium, total protein, albumin, electrolytes, VDRL, urinalysis, and for female beta-HCG)
6) For women, negative pregnancy test and use of acceptable method of contraception.

Exclusion Criteria:

1) Females who are pregnant or lactating.
2) Veterans with a current unstable medical condition such as neurological, cardiovascular, endocrine, renal, liver, or thyroid pathology (LFT ≥ 3 times normal, abnormal BUN and creatinine, and unmanaged hypertension with BP > 200/120) which in the opinion of the physician would preclude the subject from fully cooperating or be of potential harm during the course of the study (includes those with a history of seizures, glaucoma, prostatic hypertrophy, urethral obstruction, cerebral arteriosclerosis, pyloric stenosis).
3) Veterans who meet current SCID criteria for a psychotic disorder or psychosis.
4) Veterans taking Clozaril and lamotrigine. Veterans taking more than one anticonvulsant will have an additional blood draw at week 2 to more closely monitor their health.
5) Veterans with a history of allergy to zonisamide or hypersensitivity to sulfonamides.
6) Veterans already receiving CPT.

IX. Subject Recruitment and Screening

The target sample is 100 veterans diagnosed with PTSD and comorbid alcohol dependence. Veterans will be recruited from: 1) advertisement, 2) from PTSD clinics and patient units at VA Connecticut Healthcare System (VACT), and 3) from the group of patients entering treatment for alcohol use disorders at VACT Substance Abuse Treatment Program. We will review existing medical records to identify potential participants. Outreach will also be conducted to local Veteran Centers, where staff from VACT consults. The PTSD staff has also been involved in outreach to the community for returning OIF/OEF veterans. Each veteran will be carefully screened and assessed using the inclusion and exclusion criteria found above in Section 8.

X. Informed Consent Process

If a potential subject appears to meet study criteria after the completion of a brief phone screen, he or she will be scheduled for a consenting and detailed screening appointment. Subjects will complete an informed consent process and will be thoroughly screened for inclusion and exclusion criteria as described above. Any corresponding study personnel found above in Section 4 will be informing the subject about the study and obtaining signed consent. Subjects will be required to read the informed consent form in its entirety, and staff will then allow them to ask questions and have questions answered. Staff (at several time points before starting medication) will question the subject about key ethical concerns and risks of the study to ascertain whether or not the subject actually understands the risks of the study and their rights. Informed consent will be obtained in private, and subjects will be reminded that they should only participate if they truly feel motivated to do so of their own volition, and not out the influence of other parties, including their regular treatment team. Subjects will be reminded that they have the option to stop participation in the study at any point with no fear or concern about retribution from any parties. Veterans will be given a post consent test to evaluate their understanding of the procedure. For subjects who provide incorrect answers to any of the test items, the research staff will review the correct answers with the subject and show the subject where the correct answers are found in the consent form. Those who get more than 60% of the questions wrong and are still unable to understand the procedure after reviewing it with the research staff will be excluded from the study.

XI. Data Collection and Analysis

Initial assessment will include the following measures: (1) Alcohol Dependence Scale (ADS) (Skinner and Allen 1982) is a self-report measure of alcohol dependence consisting of 25 items and will be used to measure the degree of dependence and control for possible group differences in alcohol dependence. (2) Clinical Institute Withdrawal Assessment Scale (CIWA, Ar) (Sullivan et al 1989) is an interviewer driven measure of alcohol withdrawal consisting of 10 items rated on a scale from 0 to 7 and will be used to rule out withdrawal symptoms requiring medical treatment. (3) Demographic information will be collected including contact information and self-designated racial and ethnic data, in accordance with National Institute of Health guidelines.

Study Assessments will include the following: (all measures – except the CAPS which will be used every two weeks - will be administered on each study visit, every week).

(a) The Timeline Follow-Back (TLFB) method (Sobell and Sobell 1992) will be used to document the degree of daily alcohol consumption and to monitor the use of other substances during 12 weeks of treatment.

(b) Obsessive-Compulsive Drinking Scale (OCDS) (Anton et al 1995)) will be used to measure alcohol craving throughout the study. The OCDS consists of two subscales and measures obsessive and compulsive thoughts related to drinking.

(c) Clinicians Administered PTSD Scale (CAPS) will be used to obtain data on the frequency and severity of PTSD symptoms and will be administered every two weeks.

(d) Hamilton Depression Scale (HAMD) (Hamilton 1960) will be used to assess the degree and severity of depressive symptomatology. Given the overlap of PTSD and depression this scale will serve as another measure of psychiatric symptomatology.

(e) Posttraumatic Stress Disorder Checklist (PCL-C) will be used to measure PTSD symptoms every week on each visit. The PCL-C is a self-report scale that shares similar

reliability with the CAPS. (Weathers et al 1996)

(f) Modified Version of the Systematic Assessment for Treatment Emergent Events (SAFTEE) will be used to collect information on emergent side effects and their severity (weeks 1-12). This modified version will include, among other side effects, symptoms associated with zonisamide including: fatigue, decreased appetite, dizziness, headache, nausea, and agitation/irritability.

Lab Assessments will include 12-lead electrocardiogram, complete blood count, comprehensive metabolic profile, thyroid function testing, SMAC-20, urinalysis, urine toxicology screening for drugs of abuse, rapid plasma regain, gamma glutamyl transferase (γ-GGT), and serum pregnancy testing (for women of child bearing age). Blood will be drawn at baseline and weeks 4,8,12, and 25. Additionally, blood will be drawn at week 2 for veterans taking multiple anticonvulsants in order to more closely monitor their health. Urine will be measured weekly for pregnancy tests and toxicology screening.

EtG Storage and Analysis: The EtG assays will be performed at Yale in Dr. Jatlow's laboratory. The Yale group is currently characterizing the relationship between EtG concentration over time and their inter-individual and within individual variation over a range of ethanol doses (RO1AA018664) to develop more definitive cut-offs that can be used to confirm no heavy drinking. However, current knowledge of the pharmacokinetics of EtG allows the following conclusions. A concentration <100 ng/mL indicates that any alcohol consumption, even very light drinking, during the past 12 hrs. (e.g. the night before) is unlikely (Wurst et al 2006). A concentration >500 ng/mL, on the other hand refutes a self report of "no heavy drinking" in the past 1-3 days (Helander et al 2009) with several unavoidable limitations intrinsic to the pharmacokinetics of EtG. A low EtG concentration could be either consistent with light drinking during the prior 24 hours or with heavy drinking several days previously. Even light drinking on the day of the clinic visit, a short time prior to sample collection, could exceed 500ng/mL. Thus, final interpretations regarding heavy drinking for biochemical confirmation of self-report require integration with information from self-reports about the recency and quantity of alcohol consumed. Dr. Jatlow and a second reviewer will make these determinations without knowledge of the veteran's clinical course or treatment condition.

Aliquots of spot urine samples will be stored at -20 degrees within one hour of collection and subsequently transferred to a -70 degree freezer for longer-term storage. EtG will be measured using LC coupled to tandem mass spectrometry (LC/MS/MS) in the negative ion mode with deuterium labeled EtG as internal standard. This procedure, modified from published assays (Weinmann et al 2004; Wurst et al 2004) is validated and running.

Table 1. Summary of Weekly Study Assessments

Assessments	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	25
SCID I	x															
TLFB	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCDS		x	x	x	x	x	x	x	x	x	x	x	x	x	x	X

ADS	x															
Demographics	x															
CIWA	x															
CAPS Dx	x															
CAPS Sx			x		x		x		x		x		x		x	x
HAMD		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PCL-C		x	x	x	x	x	x	x	x	x	x	x	x	x	x	X
SAFTEE		x	x	x	x	x	x	x	x	x	x	x	x	x	x	X
Independent Psychiatric Exam	x															
Physical Examination	x															
Medication Count		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
EKG	x															
Medical History	x															
Labs	x				x				x				x			x
UTOX	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Data Analysis:

Descriptive statistics and graphs will be used to summarize the data on all randomized veterans. All continuous variables will be examined for adherence to the normal distribution using normal probability plots and Kolmogorov-Smirnov tests. Transformations will be applied if needed. If normality is not satisfied and transformations do not help with achieving normality alternative analytic strategies will be considered such as generalized estimating equations (GEE) or nonparametric methods for repeated measures analysis (Brunner et al 2002). For the primary hypotheses we will use mixed effects models to assess change in alcohol consumption and craving over time. Study medication (zonisamide vs placebo) and time (in weeks and months) will be used as a within-subject factors. The primary outcome drinking variable will be heavy drinking days and drinks per week calculated from the timeline data.

If significant differences between groups are observed Bonferroni adjusted post-hoc tests will be performed to test group differences at each time point. The same model will be used to examine changes in craving (using the OCDS) and PTSD symptoms (using the PCL every week and the CAPS every two weeks) over time.

XII. Labeling and Storage of Data and Specimens

All data and blood specimens will be stored without direct identifiable information, but will be identifiable via a linking code. Blood will not be used for the purpose of establishing cell lines. Any hard copy records associated with the study will be kept in locked offices. The secured research records are labeled with code numbers only (names and other identifying information are kept separate from research records). Access to hard copy data is only given to

staff members working on the study. Only staff members designated to handle or analyze study samples will have access to the samples and their storage. Coded blood samples are stored in clinic-specific refrigerators and freezers, which are located in secure rooms. As per routine all electronic files (e.g., database, spreadsheet) will be password protected. Any computer hosting such files will have a BIOS password to prevent access by un-authorized users. Furthermore, for systems not running Windows 2000/XP, a password-protected screen saver will be installed and configured to activate ten minutes after the computer has been idle.

XIII. Risk and Injury

Zonisamide

Zonisamide is approved for the adjunctive treatment of partial seizures in adults with epilepsy. Zonisamide has shown efficacy or potential efficacy in treating bipolar depression or subtypes of bipolar disorder (Anand et al 2005; Baldassano et al 2004; Ghaemi et al 2006; Kanba et al 1994; McElroy et al 2005; McIntyre et al 2002), and demonstrated efficacy in weight reduction in overweight individuals, and potential efficacy in the treatment of binge eating (Gadde et al 2003; Li et al 2005; McElroy et al 2004). It has been used as a potential treatment for alcohol use in several clinical trials, including our pilot study. The usual dose across studies is 200-400 mg. Studies suggest zonisamide is effective at 400 mg - a large ongoing clinical trial (clinicaltrials.gov) is also using 400 mg. Although in our pilot study the dose was 500mg we chose a dose of 400mg given that this study is conducted in veterans with comorbidity, and the goal is to allow subjects to also participate in E-CPT-C.

The most common adverse events observed in clinical studies (that were more common than placebo) were: fatigue (17% vs. 7% for placebo), decreased appetite (13% vs. 6%), dizziness (13% vs. 7%), headache (10% vs. 8%), nausea (9% vs. 6%), and agitation/irritability (9% vs. 4%). Although psychosis occurred at a rate of approximately 2% in trials involving patients with a seizure disorder, this was likely related to the patients' seizure disorder. There were no reports of psychosis in a trial of zonisamide for obesity. Rare or less common effects associated with zonisamide include a sensation of numbness, tingling, or prickling in parts of the body (less than 1%), a distorted sense of taste (2% vs. 0%) difficulty concentrating or remembering (4% vs. 0%), vomiting (3% vs. 0%), and trouble sleeping (3% vs. 0%). Less common, but not rare, side effects include kidney stones, which were reported in 4% of epilepsy patients taking zonisamide in combination with another anti-seizure medication in clinical trials. No kidney stones were reported during a small trial of zonisamide in the treatment of alcohol problems. Drinking an adequate amount of fluids is recommended while taking zonisamide. This may reduce the risk of kidney stones. Rare but potentially serious reactions that occurred more often than with placebo in epilepsy trials were hematologic reactions such as aplastic anemia, and severe allergic or toxic reactions. There are anecdotal reports of zonisamide worsening mood symptoms in psychiatric patients, including those with bipolar disorder. Therefore, we will monitor symptoms frequently and closely in this pilot project.

Sometimes zonisamide may cause a condition known as "metabolic acidosis" in some patients, which is a dangerous change in the acid and base balance of the blood. Generally, zonisamide will cause this condition early in treatment if it is going to occur at all, but it may develop at any time during treatment. Symptoms of metabolic acidosis are; breathing fast (hyperventilation), fatigue, and loss of appetite. More severe symptoms and risks of this condition include symptoms include an irregular heart beat, unconsciousness, and death.

Placebo

There are approved medications for the treatment of alcohol dependence and they include disulfiram, naltrexone (oral and intramuscular) and acamprosate. However, all have potential limitations, including low patient acceptability (disulfiram), modest efficacy (naltrexone), high cost and poor acceptance in treatment programs (IM naltrexone) (Petrakis et al 2003), and questionable efficacy (acamprosate). Nevertheless, in accordance with IRB policy, the alternatives to participation will be clearly described to potential veterans and those that would prefer to take these medications will be referred to an appropriate facility. Additionally, all efforts will be made to monitor adverse consequences, and to withdraw veterans from the study if clinically appropriate.

CPT

Previous research shows that PTSD symptoms may increase somewhat during the early part of CPT-C. This is expected because participants are thinking and talking more about their traumatic experience(s). However, in most instances this is a transient effect. If there is an increase in PTSD symptoms participants may receive additional support. They will be provided with a wallet card that has contact information of their clinician, and will be encouraged to call their clinician for assistance.

Venipuncture and Urine Collection

The risks of blood drawing include pain, bruising, blood clots and rarely infection. The risks are substantially decreased when performed by experienced personnel using good clinical techniques. Urine specimens are collected primarily as safeguards to veterans and should add no risks other than those normally associated with these procedures.

Measures to minimize risks

As required by the VA and Yale IRB there is a clear and detailed plan for monitoring the safety of veterans participating in this study. This protocol follows the standard VA and Yale IRB format for reporting any adverse event to the IRB and other researchers, which includes a grading system to determine if an adverse event is related to the study medication, and its severity. In addition, the PI (Ismene Petrakis, MD) will conduct a review of all adverse events upon completion of each study veteran as well as the frequency and severity of the adverse events on a quarterly basis. Frequent (weekly and more if needed) monitoring and assessment of subjects by the research team will help ensure safety and adequate management of adverse events. Adverse events will be monitored and tracked, recorded, and reported as required to the IRB, and other oversight entities if required. Strict separation of research and clinical components of the study will help to reduce bias from such sources as patients wanting either to deny continued problems, and/or to please the treatment team. Multiple sources of information will be used to detect such biases as it may occur.

This study will also be reviewed by the Monitoring Board associated with the Center for Translational Neuroscience of Alcoholism (CTNA) (a NIAAA funded grant, PI= John Krystal, MD) on a twice yearly schedule. The Data Safety Monitoring Board (DSMB) of the CTNA has

procedures that follow the National Institutes of Health (NIH) guidelines, and consists of the following individuals. Robert Swift, MD, PHD of Brown University, an expert in the clinical neuroscience of alcoholism and a practicing psychiatrist is the head of the Committee. The other members include Robert Stout, PhD of Decision Sciences Institute, Robert Hitzemann, PhD of the University of Oregon Health Center, Lisa Newton, PhD Professor of Applied Ethics in the department of Philosophy at Fairfield University and Howard Zonana, MD, Professor of Psychiatry at Yale University and Lecturer, Yale Law School.

In addition, Dr. Dolores Vojvoda will serve as the Research Monitor and her functions will include the following:

1. observing recruitment and enrollment procedures and the consent process for individuals, groups or units,
2. overseeing study interventions and interactions,
3. reviewing monitoring plans;
4. overseeing data matching, data collection, and analysis
5. discussing the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;
6. 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 IRB can assess the monitor's report.
7. shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

As noted above, precautions for pregnant or reproductive age women are in accordance with VA and Yale IRB (HIC) requirements and this will be monitored as part of the DSMP. All adverse events in the taper/follow-up time-period will be reported to the IRBs, with serious adverse events being reported within 48 hours. If during the study or at the time of tapering off of the medication the participant requires more significant care for worsening of either drinking or other psychiatric symptoms he/she may be referred to: 1) outpatient services, specific for either PTSD and/or drinking (evidence based therapy, pharmacotherapy, substance abuse services), 2) acute inpatient unit, 3)day program, 4) residential program, 5) psychiatric emergency services.

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 will 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."

XIV. Benefits

This study will not be of direct benefit to subjects. However this study may be of help in the future to veterans who have comorbid AD and PTSD.

XV. Compensation

All veterans will be compensated for their participation. Veterans will receive a check/ direct deposit payment at the end of each appointment: $20 at the screening appointment, $30 baseline appointment, $30 at each weekly appointment, $50 for the Week 12 assessment, $30 for the Week 13 assessment, $30 for the Week 14 assessment, and $30 for the follow-up. Veterans can receive up to a total of $520 if attending all scheduled visits.

XVI. Confidentiality

All reports generated from this study will not contain any identifying information about the participants. Research records are coded only by a number, and are stored in locked cabinets. Consent forms, release of information forms, and research nurse medical charts will be kept locked in a place separate from subject data collection forms. Subjects will be informed that medical evaluations, including physicals, EKGs, and urine/blood tests will be administered through the hospital and will become part of their permanent record. Finally, subjects will be informed that a hard copy of the consent form will be placed in their paper record. An electronic progress note citing their participation in this research study will be entered in their electronic chart upon entry into and exit from, the study.

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

XVII. Literature Review

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