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2. Title of the project:
"Effectiveness of Zonisamide in Treating Alcohol Dependent Veterans"

3. Purpose, hypothesis and key questions

Purpose: To study the effectiveness of an anticonvulsant medication (zonisamide) for the treatment of alcohol dependence in veterans. We want to see if the medication works to reduce harmful heavy drinking, and try to determine whether medication response can be predicted by a few key factors such as genotype and the age of onset of alcoholism (early vs. late).

SPECIFIC AIMS: Alcohol use disorders (AUDs) have a substantial public health impact in the United States, costing billions of dollars every year. AUDs are highly prevalent in veterans, including those who have returned from service in Iraq and Afghanistan, 9.9% of whom experience AUDs post-deployment, a higher rate than for civilians. Studies of Vietnam-era veterans have estimated the lifetime prevalence of AUD to be almost 40% for men. There is also a high rate of co-occurring psychiatric illness in returning veterans with AUDs, most notably anxiety and mood disorders. The Food and Drug Administration (FDA) has approved four pharmacologic agents (naltrexone, naltrexone monthly injection, acamprosate, and disulfiram) for the treatment of alcohol dependence (AD), but they are limited by their questionable efficacy in veterans (naltrexone and disulfiram) and in the general population (acamprosate). The development of medication to reduce drinking is a priority for military personnel and veterans, who are often dually diagnosed (i.e., have psychiatric illnesses such as mood or anxiety disorders in addition to AD).

Zonisamide (ZNS), an anticonvulsant acting on serotonergic, dopaminergic, GABAergic, and glutamatergic neurotransmitter systems, has shown great promise in treating individuals with AD. We conducted a pilot study (N = 40) showing that ZNS, given once daily, significantly reduced heavy drinking and overall drinking compared to a placebo in subjects with AD and was very well tolerated (Arias et al., 2010). Several anticonvulsant medications have shown promise in treating alcohol dependence, most notably topiramate, but ZNS has advantages over topiramate, including a more favorable side effect profile and a simpler once-a-day dosage regimen. ZNS also has direct pharmacologic action on dopamine and serotonin, which may make ZNS particularly effective in treating co-occurring psychiatric disorders. Topiramate's effectiveness is limited by its poor tolerability, so better tolerated medications are needed.

DESIGN: We propose a 16-week randomized, double blind, placebo-controlled trial designed to determine the effectiveness of ZNS treatment for reducing heavy drinking and overall drinking in 160 treatment-seeking, regularly heavy drinking, alcohol-dependent veterans who want to quit drinking or reduce consumption to non-hazardous levels. We will use state-of-the-art methodology and outcome assessments, including medical management (MM) therapy (a minimal behavioral intervention aimed at reinforcing treatment goals and adherence to medication), which is simple and easily implemented in primary care settings. The use of MM in the study will increase the generalizability of results, allowing a more accurate assessment of ZNS's effectiveness than if a more intensive behavioral intervention were to be used. To demonstrate ZNS's effectiveness in a representative veteran sample, we will include veterans with co-morbid mood and anxiety disorders.

We also plan to explore the interaction between genotype and medication on drinking outcomes, targeting two functional polymorphisms: The first SNP is in the gene *DBH*, and we have found that it moderates the treatment response to naltrexone in veterans. The other is a functional variable number, tandem repeat (VNTR) polymorphism located in exon 3 of the DRD4 gene that has been shown previously to moderate the effects of medications on drinking behavior. Both polymorphisms are directly relevant to ZNS's mechanism of action and alcoholism pathophysiology.

Specific Aim 1 (Primary Aim): To determine the effectiveness of ZNS treatment in reducing drinking on the primary outcome measure: drinks per week (measured using the Timeline Followback Method), for eight weeks at a target dose of 600 mg of ZNS daily for 160 heavy-drinking, alcohol-dependent veterans. We hypothesize that ZNS treatment will reduce the heavy drinking days per week and the total drinks per week significantly more than the placebo and that the benefits will persist at three months follow-up after treatment.

Specific Aim # 2 (Secondary Aim): To examine the effects of ZNS treatment on heavy drinking days per week, , percentage of subjects with no heavy drinking days (PSNHDD) the urge to drink (craving), biomarkers of alcohol intake, clinical global impression, medication tolerability, and other patient-centered outcomes. We hypothesize that ZNS will demonstrate significantly greater improvements than the placebo on these measures by the treatment endpoint as well as at follow-up.

Specific Aim #3 (Secondary): To use telephone-based daily process data collection to elucidate the mechanism of action of ZNS as it relates to changes in craving, anxiety, and genetic variation. *This method has been shown to elucidate the mechanism of action of topiramate, as well as its pharmacogenetic interactions*. We hypothesize that ZNS' effects will be moderated by genetic variation, craving, and anxiety, but mediated through changes in self-efficacy to reduce heavy drinking.

Specific Aim #4 (Exploratory): The exploratory aim is to examine the pharmacogenetic interactions between ZNS and the therapeutic response. We hypothesize that both the long (L) allele of the VNTR polymorphism in exon 3 of the *DRD4* gene and the CC genotype of the *DBH* rs1611115 (C-1021T) SNP will show a pharmacogenetic effect with ZNS, as evidenced by a greater reduction in drinking than for the short (S) allele and T carriers respectively.

Specific Aim #5 (Exploratory) To compare ZNS and placebo-treated subjects on pre- and post-treatment changes in measures of stress-reactivity (i.e., stress-induced anxiety, alcohol craving, autonomic nervous system activity), cue-elicited craving, and impulsivity. We hypothesize that ZNS will attenuate stress-reactivity, cue-elicited craving, and impulsivity more than placebo in a stress laboratory paradigm, and that attenuation of those measures will be associated with reduction in drinking.

4. BACKGROUND:

4.A. Introduction: Alcoholism continues to be a prevalent public health concern with a large impact on society, including veterans (1-3). Alcohol use disorders are highly prevalent in veterans, many of whom never receive evidence-based medication treatments to reduce drinking. The FDA approved medication treatments for alcoholism (naltrexone, acamprosate, disulfiram) have a limited effect, and pharmacologic treatments with greater efficacy are needed (4). Anticonvulsants have shown some effectiveness in treating alcoholism; among these is zonisamide (ZNS), an anticonvulsant that modulates the GABAergic, glutamatergic, dopaminergic, and serotonergic neurotransmitter systems involved in the pathophysiology of alcohol dependence (AD). ZNS is a promising new potential treatment for treating AD and it appears to have advantages over existing pharmacologic treatments for AD, including its easy once a day dosage, its favorable side effect profile, its promotion of healthy weight loss, a likely stronger effect on reducing drinking in early onset alcoholics, and its potential benefits for mood and anxiety disorders. Veterans with AD often have an early onset of the disease, and frequently have co-occurring psychiatric illnesses, thus ZNS is a good choice for treating them.

4.A.1. Veterans Have High Rates Of Alcoholism And Co-Occurring Psychiatric Illnesses:

Alcohol use disorders (AUDs; these can refer to either abuse or dependence) are highly prevalent in veterans, with an estimated current prevalence of 9.9% in returning Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) veterans (5). The study by Seal reported a point prevalence for current AD of 5.2% in returning veterans, which is greater than the estimate for civilians of 3.8% (2). The rates observed by Seal and colleagues were similar to those observed in Vietnam era veterans; however, the lifetime prevalence for Vietnam era veterans was much higher when examined approximately 15 years after the end of the war, at almost 40% in men (6). A recent study by researchers affiliated with the National Center

for PTSD confirmed this estimate in a more recent independent sample (unpublished). The lifetime prevalence of AUDs in civilians, in contrast, is approximately 30% (2). Thus the prevalence of AUDs (including AD) is at least as high (and probably higher) in veterans than in the civilian population.

Returning OEF/OIF veterans under the age of 25 have the highest rates of AUDs when compared to older veterans, at approximately 9%, and thus the rates of early onset alcoholism (EOA) are likely very high in these veterans. This is important to note because EOA is often associated with greater psychiatric co-morbidity, and is often thought to be more difficult to treat. Patients with EOA respond variably to medications for alcoholism (7, 8). Anticonvulsants, like ZNS, may work best for those with EOA.

Seal et al. (2011) also observed high rates of co-occurring addictive and psychiatric illness, with 55-75% of subjects with an addictive disorder also having either posttraumatic stress disorder (PTSD) or depression. Those with PTSD or depression also had a 3-4.5 times higher risk of developing an addictive disorder. ZNS may be of benefit in the treatment of co-occurring mood and anxiety disorders in veterans with AD.

4.A.2. Alcohol Dependent Veterans Need New And Better Treatments:

Research on medications to treat AD in real-world, representative veteran populations is greatly needed. The available literature indicates only limited support for the use of existing medication treatments for AD in veterans. Psychosocial behavioral interventions have efficacy, but a large proportion of patients with AD relapse within one year without adjunctive medication treatment (9). A large cooperative multi-center study evaluated the efficacy of naltrexone in veterans, but the medication was not found superior to a placebo (10). Disulfiram efficacy was studied in a large sample of veterans with AD, and was again not found superior to a placebo (11). Acamprosate efficacy is supported by meta-analysis, but several large studies performed in the United States have shown negative results (12-14). Effectiveness data for acamprosate in veterans is lacking, and adherence to the three-times-daily dosage regimen proves difficult for these patients. Several studies that compared the effectiveness of acamprosate to disulfiram and naltrexone have found acamprosate to be inferior (15-17). Dr. Petrakis (a co-investigator on this application) completed a Mental Illness Research, Education and Clinical Centers (MIRECC) sponsored multi-site effectiveness study of dually-diagnosed veterans with AD, and showed a small benefit of medication use (naltrexone, disulfiram, or the combination) compared to a placebo (18). This study is important because it shows the potential usefulness of adding medication to the existing treatment regimens of veterans in a representative population. Nevertheless, the effect was modest, suggesting that better medications are needed. Veterans face unique social and economic challenges, and more research is needed to evaluate the effectiveness of pharmacotherapies in this population. The proposed study will address this knowledge gap, and will work towards developing better treatments.

4.A.3. Addressing Critical Barriers To The Use Of Pharmacologic Treatments For AD In Veterans:

Medication treatment of AD has not been widely adopted by physicians, including those within the VA Healthcare system. Studies by Mark et al. (2003) in the civilian population and by Harris et al. (2013) in the VA healthcare system found convergent evidence that a perceived lack of research into medications (by clinicians) is a barrier to medication use in practice. Furthermore, a survey of the VA providers by Harris et al. (2013) indicated a perception among respondents that one of the best strategies to eliminate this barrier was to perform more research on medication treatments for AD. A trend toward improvement has emerged within the VA healthcare system, but still only 3.4% of veterans with an AUD received any medication to treat the disorder (19). Another barrier to medication treatment for AD is perceived side effects (20). ZNS is well tolerated and likely is better tolerated than are some other available treatments for reducing drinking, such as disulfiram, or topiramate. The beneficial effect of ZNS on weight loss offers an additional incentive to many patients, and may facilitate adherence when compared to other medications.

4.A.4. Breaking Through Barriers To Effective Treatment With Personalized Medicine For Veterans:

As noted previously, returning veterans have high rates of EOA. Our pilot study indicated that ZNS was particularly effective at reducing heavy drinking in subjects with EOA. This is detailed further in the Preliminary Studies section. The exploratory pharmacogenetic work proposed in this study may help overcome barriers to medication use in practice by providing physicians with a way to personalize treatment, thereby optimizing effectiveness and reducing adverse reactions to medication.

4.B. ZONISAMIDE: An Innovative And Unique Pharmacologic Agent For Treating AD

4.B.1. Treating Alcoholism with Anticonvulsants and ZNS:

The potential utility of anticonvulsants to reduce the risk or severity of relapse was demonstrated initially in a 12-month pilot study of carbamazepine by Mueller, Stout (21), who found the drug to be superior to a placebo with respect to a number of drinking outcomes. A 12-week, double blind, placebo-controlled pilot study of divalproex in alcohol-dependent individuals by Brady, Myrick (22) showed that divalproex reduced irritability and had a slight effect on reducing the risk of relapse into heavy drinking when compared with a placebo treatment. Johnson, Ait-Daoud (23) demonstrated the efficacy of topiramate for AD in a double blind, randomized, placebo-controlled trial. In a follow-up, larger (N=371), multi-center, randomized placebo-controlled trial (24), topiramate was again found superior to a placebo with a moderate effect size. This fourteen-week trial of topiramate, with dosage up to 300mg/day, showed an effect size of 0.52 in the reduction of the percentage of heavy drinking days for treatment-seeking alcoholics who received 14 weeks of concomitant brief behavioral compliance therapy (a minimal behavioral intervention aimed at enhancing medication compliance) (4).

A more conservative analysis of the topiramate data, which assumed a return to baseline drinking levels for dropouts, reduced the effect on percentage of heavy drinking days by almost half (a difference in mean reduction of 16.19% of heavy drinking days compared to 8.44% reduction in the conservative analysis), and some critics have brought attention to the frequency and severity of side effects of this medication, which limits its use and effectiveness (24-26). Thus, although topiramate is effective, its use is significantly limited by its side effects. Research demonstrating effectiveness of topiramate in veterans is lacking. A recent study in civilians showed a moderate dose of topiramate to be fairly well tolerated and efficacious (27).

Recently, a placebo controlled trial of the anticonvulsant gabapentin for civilians with AD showed significant benefit with the medication, although the dropout rate was high (28). Gabapentin often requires a three-times-daily dosage regimen, which decreases the likelihood of adherence in patients. In contrast, ZNS has a long half-life and is easily administered once daily.

4.B.2. The Rationale For ZNS Treatment Of AD In Veterans:

In addition to the reasons described in section A of this application, strong support is available from animal models for the use of ZNS to treat veterans with AD. Positive results from human laboratory and pilot clinical trials also have demonstrated clinically significant reductions in drinking with ZNS treatment. ZNS is FDA approved for the adjunctive treatment of partial seizures in adults with epilepsy. Rats chronically administered topiramate or ZNS showed reduced consumption of an ethanol-sucrose solution (29). Three small clinical trials have examined ZNS effects on alcohol consumption in humans, **one of which was the placebo-controlled pilot study that we recently completed (30).** The other two clinical trials were open-label (31, 32) and reported findings that agreed with those of our placebo-controlled trial by showing reduced drinking and craving with the medication, plus a favorable safety profile. A small human clinical study of alcohol self-administration and a one-time dose of ZNS in risky drinkers showed a reduction in urge to drink and in the amount of alcohol consumed with ZNS compared to a placebo (33). A trial comparing ZNS to diazepam in treating alcohol withdrawal syndrome found ZNS to more effective than diazepam, and that subjects had less alcohol craving, less anxiety, and less sedation (34). In these studies, ZNS was well tolerated, and few participants dropped out.

Initial findings with ZNS are promising, both in terms of its tolerability and its potential efficacy in reducing drinking behavior in alcoholics. We found a small effect size for measures of heavy drinking reduction, and a medium effect size for overall drinking reduction; however, these effect size estimates are likely conservative, as the use of cognitive behavioral therapy (CBT) in both groups may have introduced a ceiling effect, thereby reducing the observed effect sizes. **These findings of the potential benefits of ZNS for the treatment of AUDs strongly support further study of ZNS in order to advance the treatment of the disorder.**

ZNS has also has shown some evidence of efficacy in treating anxiety disorders, major depression, bipolar depression, and subtypes of bipolar disorder (35-38). It also shows efficacy in weight reduction in overweight individuals, and potential efficacy in the treatment of binge eating (39-42). Since veterans with AD have high rates of co-occurring psychiatric illness, the effects of ZNS on reducing drinking and improving mood and anxiety symptoms indicate it to be a good choice for treating them.

For the current study, we will include subjects with depressive disorders (including unspecified and type II bipolar disorder, but not a history of bipolar disorder type I), sub-syndromal and full syndrome PTSD, and other anxiety disorders.(31, 32)

4.B.3. ZNS Acts On The Major Neurotransmitter Pathways Involved In Alcoholism:

ZNS has a unique and multifaceted pharmacological profile causing facilitation of dopaminergic, serotonergic, and GABAergic neurotransmission, while attenuating glutamatergic transmission. **The most**

unique actions of ZNS are its effects on the GABA reuptake transporter GAT-1, and its reversible Monoamine Oxidase-B (MAO-B) inhibition. ZNS blocks sodium channels, and inhibits carbonic anhydrase (43). ZNS indirectly facilitates GABA and reduces glutamate neurotransmission, unlike the direct effect exerted by topiramate on GABA-A, AMPA, and kainate receptors (44, 45). Topiramate is thought to block L-type calcium channels, and ZNS is thought to block T-type calcium channels (43). ZNS also appears to have direct and biphasic effects on the neuronal release of both dopamine and serotonin (46, 47). ZNS increases GABAergic output and attenuates glutamatergic neurotransmission with continued administration, so that it may reduce both the rewarding effects of alcohol consumption and the unpleasantness of drinking cessation, including alcohol urge or "craving." ZNS is an effective adjunct therapy for Parkinson's Disease, an observation attributed to its pro-dopaminergic effects via increased production and output of dopamine in the striatum. This includes a reversible MAO-B inhibitory effect, which is neuroprotective against metabolic stressors (48, 49). Reversible MAO-B inhibition and ZNS are not associated with the side effects attributed to irreversible MAO inhibitors, and hypertensive crises or dietary restrictions are not concerns. This reversible MAO-B inhibitory effect may explain the beneficial effects of ZNS on mood and anxiety. ZNS has direct effects on serotonergic and on dopaminergic neurotransmission, which are both involved in the pathophysiology of alcoholism (46, 47, 50, 51). ZNS increases serotonergic and dopaminergic output over time, an effect that is biphasic in terms of dose relationship; therefore, at a certain point, output of these neurotransmitters starts to levels off although output remains elevated relative to baseline. This effect of ZNS may help stabilize these systems in the brains of alcoholics.

4.B.3.a. ZNS Effects on GABAergic and Glutamatergic Neurotransmission:

Alterations in GABAergic and Glutamatergic neurotransmission due to chronic alcohol exposure are thought to contribute to neuroplasticity throughout the brain. This is perhaps most important in the ventral striatum and its closely connected systems, commonly referred to as the so-called "reward system" (50). Glutamatergic interactions with dopaminergic pathways are considered key and likely necessary components in the process of maintenance of addiction to drugs and alcohol (52). Ethanol modulation of GABAergic neurotransmission, and in particular $GABA_A$ receptors, is a major component of alcohol effects in the brain and a main contributor to the pathophysiology of alcoholism (53). ZNS allosterically binds but does not directly modulate $GABA_A$ receptors (43). ZNS effects on GABAergic neurotransmission are highly complex, but ZNS appears to facilitate GABAergic inhibitory neurotransmission overall while reducing glutamate release from neurons (45).

ZNS also acts on Excitatory Amino Acid Transporters (EAATs), which are membrane bound glutamate transporters thought to be responsible for perisynaptic clearance of glutamate as well as clearance from the surrounding extracellular "bath." Potential involvement of EAATs has been proposed in the pathophysiology of AD. (54). In the hippocampal and frontal brain areas of rats, ZNS treatment upregulated and enhanced the function of the glutamate transporter EAAT3/EAAC1 and down regulated the GABA reuptake transporter GAT-1 (44). By this mechanism, ZNS increases glutamate clearance and potentiates GABAergic transmission by increasing tissue and synaptic GABA levels. Thus ZNS may benefit the treatment of AD via attenuation of glutamatergic transmission while facilitating GABAergic transmission.

4.B.3.b. ZNS Pharmacokinetics: ZNS is almost completely absorbed with a time to peak concentration of 2-6 hours (55). ZNS bioavailability is not affected by food although the time to peak concentration may be delayed. The volume of distribution in adults is 1.45 L/Kg, and it is largely (40-60%) protein bound in erythrocytes (56, 57). Hepatic metabolism of the drug occurs with acetylation of ZNS to N-acetyl ZNS and CYP3A4 mediated reduction to 2-sulfamoylacetyl phenol (SMAP). About 60% of the drug is recovered in urine, about half of it as parent compound (ZNS) and half as metabolites. The plasma elimination half-life is about 63 hours. ZNS penetrates the blood-brain barrier and the ratio of cerebrospinal fluid ZNS to plasma ZNS is .76. Metabolism and clearance of ZNS is increased in subjects taking enzyme-inducing medications. ZNS does not appear to be an inducer or substantial inhibitor of P450 microsomal enzymes. Steady state levels are achieved within 14 days from achieving a stable target dose. Patients with significant renal or hepatic disease may require adjustment in ZNS dosing and titration. Note that subjects with significant renal or hepatic disease will not be included in this study (refer to methods section, exclusion criteria).

4.B.3.c. ZNS Dosing Rationale: ZNS is typically used efficaciously in the range of 400-600mg/day in adults with seizure disorders as an adjunctive treatment (58). Similarly, clinical trials for weight reduction in obesity, and for treatment of binge eating disorder have employed ZNS target doses in the range of 400-600mg/day

(39, 40, 42, 59). For our pilot study of ZNS, the target dose was determined based on extrapolation from the aforementioned studies, and a comparison to the efficacious dosing of topiramate in studies for the treatment of alcoholism and weight reduction. The mean maximal dose of ZNS in the pilot study was 430mg/day. Topiramate appears to be efficacious in reducing weight, binge eating, and drinking in the range of 200-300mg/day, though significant weight loss can occur at lower doses (23, 24, 60-63). For the pilot study of ZNS in the treatment of alcohol dependence, a target dose of 500mg/day was selected based on ZNS's general clinical behavioral similarity to topiramate at an approximate analogous 2:1 dosing equivalency between the two medications with regard to appetitive behaviors. The data from the ZNS pilot study suggest that a slightly higher dose of 600mg daily may optimize the effect of the medication on reducing drinking, and that the higher dose would likely be well tolerated. Titration rates of 100mg every 1-2 weeks have been used safely in studies to date.

4.B.3.d. Innovation Through Translational Research: Pharmacogenetics and Treatment of AD:

Genetic variation is thought to influence the subjective and physiologic response to alcohol and medications. Knowledge concerning pharmacogenetic responses to alcohol could help us to individualize treatment regimens for AD, thereby improving treatment outcomes and reducing the risk of adverse effects. Additional scientific knowledge is greatly needed regarding variation in individual response to medications for alcoholism treatment in order to develop personalized treatments and to increase treatment effectiveness.

4.B.3.e. Identifying candidate polymorphisms for studying ZNS pharmacogenetic interactions: There are few data to guide this exploratory analysis of ZNS pharmacogenetics. We have selected a polymorphism in the DBH gene that has been shown to moderate the treatment response for drinking cessation with other medications. DBH is the gene that encodes the enzyme dopamine beta-hydroxylase, which converts dopamine to norepinephrine, and is located on chromosome 9q34. It is expressed in the ventral striatum. DBH rs1611115 SNP (-1021C➔T) is a functional, non-coding, intronic SNP that consists of a variant T allele (C/T), and is located near the initiation codon of DBH (64). This SNP is associated with lower plasma levels of dopamine beta-hydroxylase expression, and also with the personality traits of aggression and impulsivity (64, 65). One recent study showed that it was associated to the risk of developing AD with comorbid psychiatric traits (66). We recently found that this SNP moderates the response to naltrexone in alcohol dependent dually diagnosed veterans (see preliminary studies). The SNP also moderated the response to disulfiram treatment for cocaine dependence (67). We hypothesize that the CC genotype of the DBH rs1611115 (C-1021T) SNP will show a pharmacogenetic effect with ZNS, as evidenced by a greater reduction in drinking than for T carriers.

5. Significance:

Veterans have a high prevalence of alcohol dependence (AD), and those with AD also have a high rate of co-occurring psychiatric illnesses. Zonisamide is an extremely promising medicine for treating AD and managing other clinical problems including psychiatric disorders. Zonisamide is an affordable, generic anticonvulsant with unique actions on the major neurotransmitter systems involved in alcoholism, and it has neuroprotective effects. We recently completed a randomized, placebo-controlled pilot study of zonisamide in treating AD that showed significant reductions in heavy drinking, overall drinking, and alcohol craving. Zonisamide was very well tolerated in this study. In this application, we propose a larger (N = 160), 16-week, randomized, double-blind, placebo-controlled, effectiveness study of zonisamide in reducing heavy drinking and improving outcomes in a representative population of heavy-drinking veterans with AD.

6. RESEARCH PLAN/EXPERIMENTAL METHODS:

6.A. CLINICAL TRIAL METHODS:

OVERVIEW:

Specific Aims 1- 5, Effectiveness of ZNS in the Treatment of Alcohol-Dependent Veterans: We propose to conduct a 16 week, randomized, double blind, placebo-controlled study of ZNS in ***N=160*** regularly heavy drinking veterans with AD in the context of a minimal ambulatory psychosocial treatment aimed at enhancing adherence to medication (Medical Management, MM), (68). We will recruit and enter ***160*** subjects with which the study will be adequately powered. *All subjects must be currently alcohol dependent. The target dosage for ZNS is 500mg/day, which will be titrated up over the first 7 weeks of treatment, with dosage increases based on tolerability. The titration schedule will start with 100mg daily, increased to 200mg/day after the first week,*

*and then increased by 100mg/day every 2 weeks to the **target dose of 500mg/day**.* Subjects will then begin 9 weeks at the target dose with the option to increase to 600mg daily after two weeks at target if treatment response is suboptimal and there are no significant side effects (no current moderate to severe AE's with 500mg daily). Dosing will remain flexible with respect to the time of day that the medication is administered, in order to maximize compliance and minimize the impact of adverse effects. The dosage will be held or reduced based on the appearance of moderate-to-severe adverse effects. **Following the seven week titration phase, subjects will begin the 9 week period of active treatment on the target dose, followed by up to 2 weeks of tapering and discontinuation of the medicine, and a return for follow-up at three months post-treatment. The dosing is also flexible in that it will allow subjects to continue on at less than the target dose based on tolerability, but subjects must be able to tolerate at least 200mg/day (two pills). Also, if subjects are not having moderate to severe side effects during the treatment phase, and have not yet reached 600mg/day, they may be increased by up to 100mg every 2 weeks if it is felt that they may benefit further from it. This will allow maximum flexibility and optimal dosing.**

Daily reports obtained using IVR will be used to identify subjective correlates of medication effects (e.g., craving) and to monitor medication use. A half-day long "stress response" laboratory session based on that developed by (69) will be performed with subjects, if their schedule allows, after screening but before starting medication (baseline stress/impulsivity), and then a second lab will be performed between weeks 8-16.

6.B. Subjects *and recruitment*: The study is being conducted at two sites; (1) the West Haven VAMC, also known as VA Connecticut Healthcare System (VACHS), at our Alcohol Research Center (VAARC); and (2) the Bedford VAMC in Massachusetts. We have had successful collaborations between these two sites previously, and both have good records of subject recruitment.

6.C. Inclusion and Exclusion Criteria: *N=160* men and women **veterans** are being recruited through referrals, flyers at VA facilities, and from among participants in prior studies in the VAARC. Each subject must meet all of the following ***inclusion criteria*** to participate: a) age 21-70 years, inclusive; b) regular heavy drinkers as defined by averaging 1 heavy drinking days per week over 90 days baseline pre-treatment timeline follow-back (TLFB), and ***current DSM-IV-TR alcohol dependence*** that recognize a need to reduce or stop drinking (**Note:** heavy drinking days will be defined as follows; for men greater than or equal to 5 drinks in a day and for women greater than or equal to 4 drinks in a day); c) women of child-bearing potential (i.e., no hysterectomy, bilateral oophorectomy, or tubal ligation or <2 years postmenopausal), must be non-lactating, practicing a reliable method of birth control, and have a negative serum pregnancy test prior to initiation of treatment; d) willingness to provide signed, informed consent to participate in the study.

Exclusion criteria are: a) a current, clinically significant physical disease or abnormality (i.e., neurologic, renal, rheumatologic, gastrointestinal, hematologic, pulmonary, endocrine, cardiovascular, hepatic, or autoimmune disease that, in the context of the study would represent a risk to the subject, or significant laboratory abnormalities **such as hepatic aminotransferase levels (i.e., AST and ALT) greater than 300%** of the upper limit of normal or direct bilirubin levels >150% of the upper limit of normal) on the basis of medical history, physical examination, or routine laboratory evaluation. Other specific exclusionary disorders include; b) history of renal calculi or renal failure; a significant indication of renal compromise will be defined by an elevation of serum creatinine above our laboratory's limit of normal, or a known history of renal failure or chronic renal disease, or any current or chronic disease that could reasonably be expected to result in renal failure c) history of hypersensitivity to ZNS or any sulfonamide, Stevens-Johnson Syndrome, penicillin allergy, or history of any severe drug allergic reaction; d) history of systemic autoimmune disease such as lupus erythematosis, fibromyalgia, or rheumatoid arthritis; e) current blood dyscrasia or a history of such, with the exception of a past history of iron deficiency anemia; f) history of seizure disorder; g) regular use of any of a number of medications that might prominently influence drinking patterns or cause risk of harm or injury (**e.g., , benzodiazepines, acetazolamide, chronic use of opioid pain medications**; i) schizophrenia, bipolar type I disorder, or substantial suicide or violence risk (i.e., can't be managed safely in the outpatient setting) on the basis of history or psychiatric examination; j) currently dependent on opioids or benzodiazepines or other sedatives; k) considered by the investigators to be clinically inappropriate for study participation or have participated in another pharmacotherapy study in the past thirty days; l) subjects with prominent signs of physical dependence, and/or medical comorbidities such that study physicians feel they should consider immediate detoxification, and referred for medical detoxification in a normal treatment setting; m) patients who report having 5 or more standard drinks within 24 hours of urine ETG sample collection at screening will be

excluded if their ETG levels are negative.. The Clinical Institute Withdrawal Assessment (CIWA-Ar) will be used to facilitate assessment of withdrawal, and decisions regarding appropriateness for study entry with respect to physical dependence will be made based on the judgment of study physicians using a the CIWA-Ar score of 10 for an approximate cutoff level. All our study physicians have extensive experience in assessing and triaging patients with alcohol withdrawal. Subjects that need detoxification will be referred for detoxification, and may be eligible to begin the study following successful completion of detoxification.

6.D. Study Periods:

6.D.1. Visit 0 (Screening Visit): At screening visits, subjects are asked to provide informed consent and a screening number will be assigned. A medical and psychiatric history obtained from subjects. Drinking data for the 7 days prior to the screening visit will be collected via the Timeline Follow-Back (TLFB) Method Blood and urine samples are taken for routine clinical laboratory evaluations (complete blood count, serum chemistry panel, urinalysis, gamma-glutamyltransferase (GGT) concentration), and screening for drugs of abuse, and pregnancy testing (in all females of reproductive potential) will occur. If no medical problems are identified that would limit the subject's participation, he/she will be administered the Structured Clinical Interview for DSM-IV (SCID-I) to identify current and lifetime psychiatric disorders. Either at the screening visit, or between the screening and baseline visit, a physician or nurse practitioner will do a complete medical history and physical on the subject. Alternatively, if subjects have had a complete medical physical completed at the VA within the last 30 days (for example, by their primary care doctor), we will use that exam to qualify them for the study.

6.D.2. Visit 1 (Baseline Visit): N= *160* subjects will be randomly assigned to receive either ZNS (80 subjects) or placebo (80 subjects). We will use blocked stratified randomization with treatment site (VA Connecticut versus Bedford) and the use of other psychotropic medications (e.g., antidepressants) as the stratification variables, with block sizes of 4 in each stratum to achieve treatment balance throughout the randomization process. Within 21 days after the screening visit, eligible subjects undergo a two-hour pre-treatment assessment (described below). At the baseline visit, subjects will complete a packet of questionnaires. Subjects will receive their first medication management session and first supply of study medication during a treatment session (visit 1) scheduled on the same day, following completion of the baseline assessments.

Subjects will begin study medication (i.e., ZNS or matching placebo) at an initial dosage of 100mg/day. All subjects will be asked to bring any remaining capsules and the study medication container to their next and all subsequent clinic visits, so that capsule counts can be used to measure compliance. The subject begins 6-week titration phase, during which the dosage will be titrated up as indicated above and in Table 1. Subjects will be paid a nominal but fair amount of money in compensation for all visits, including follow-up visits. Table 1 shows the titration schedule:

TABLE 1: Medication Titration Schedule

Week	***Placebo***	***Zonisamide dose***
1	**One capsule daily**	**100mg QHS**
2	**Two capsules daily**	**200mg QHS**
3	**Two capsules daily**	**200mg QHS**
4	**Three capsules daily**	**300mg QHS**
5	**Three capsules daily**	**300mg QHS**
6	**Four capsules daily**	**400mg QHS**
7	**Four capsules daily**	**400mg QHS**
8-9	**Five capsules daily**	**500mg QHS (Target dose)**
10-16	**Five or Six capsules daily, 7 weeks duration**	**Continue 500mg daily or optional increase to 600mg QHS, 7 weeks duration**
17-18	**TAPER: Decrease capsules by one a day every 3 days, over a period of up to 15 days**	**TAPER: Decrease dose 100mg every 3 days, over a period of up to 15 days**

Table 1 notes: 7 weeks of titration to the 500mg daily target dose. 9 weeks at the target dose with the option to increase to 600mg daily after two weeks at target if treatment response is suboptimal and there are no significant side effects (no current moderate to severe AE's with 500mg daily).

6.D.3. Visit 1b (Baseline stress response lab): *THIS LAB SESSION IS DESCRIBED IN FULL DETAIL BELOW IN SECTION 6.H*. Subjects will be scheduled for this ~ 3-hour session to occur after being screened and giving informed consent. This paradigm is based on that developed by Dr. Rajita Sinha which uses mental imagery techniques to examine the response to stress, though we have condensed it into a one lab session. Staff will help subjects to develop three 5 minute long scripts that will be read and audiotaped; one describes a very stressful event in the person's life, one describes a neutral event, and one describes a pleasant alcohol-related event. Then subjects sit in an isolation booth and listen to the audio tapes sequentially while psychological measures of craving, anxiety, and impulsivity/risk-taking [via the Balloon Analogue Risk Task (BART)] are recorded (70). Subjects are taught to relax for approximately ten minutes between each audio tape script listening session, and measures are repeated identically for each of the three tapes. This entire lab session will be repeated again with an additional visit (10b) occurring between weeks 8-16 of being on the medication. Baseline impulsivity will also be measured before imagery using the Barrett Impulsivity Scale (71). Patients will be paid $50 for each of the two sessions. All subjects enrolled at the VACT site will have their lab sessions at the West Haven VAMC where we have successfully run a similar protocol. *Note that we will try to have all participants undergo the stress labs, however, if it is too burdensome due to the subject's schedule, we will still allow them to participate in the clinical trial without completing the stress lab.*

6.D.4. Visits 2-17 (Treatment and End-of-Treatment Visits): Subjects will return weekly for study visits to meet with the research nurse, complete questionnaires, and receive medical management (MM, described below). At study midpoint (i.e., 8 weeks after starting medication), another CBC, and chemistry/electrolyte panel (including a serum GGT), will be obtained. Urine drug screens will be checked weekly, and pregnancy tests (in all females of reproductive potential) are repeated monthly. At the end of week 16 (endpoint), subjects will complete the packet of questionnaires and will be interviewed by the research evaluator concerning their alcohol-related symptomatology using the Alcohol Use Disorders section of the SCID over the past 30 days. Subjects will also be interviewed by the research nurse about their use of concomitant medications, occurrence of adverse events, compliance with the protocol, and their assessment of the effectiveness and acceptability of the treatment procedures. A blood sample for measurement of serum GGT and metabolic labs will be obtained to provide an index of potential hepatic effects and to assess the validity of self-reported drinking. A urine drug screen and urine pregnancy screen (in all females of reproductive potential) will be obtained at this time as well. The nurse and study physician will monitor continuing adverse events to their resolution. Subjects requesting (or clearly needing) additional treatment for alcohol problems are (if clinically indicated) discontinued from the study protocol and referred to local treatment centers. Similarly, at the end of the treatment trial, subjects whose drinking requires continued treatment will be referred for such treatment. All subjects will be asked to complete an end-of-treatment evaluation to facilitate planned intention-to-treat analyses. All subjects will be informed of these procedures prior to study enrollment.

6.D.5. Visit 10b (Stress Lab Session 2): This visit will occur between weeks 8-16 of being on the study medication. The session will use the same audio tapes created for the baseline stress lab and the session will be identical to the baseline stress lab (assessments), with the exception of the randomized order of the presentation of the audio tapes.

6.D.6. Visit 18 (Tapering Medication Checkup): *This occurs two weeks after the endpoint visit (see TABLE 3 below in section #8).* Study medication will be tapered off over approximately 2 weeks. ZNS (or placebo) will be reduced by 100mg every three days until stopped. Subjects will be asked to return to the clinic 2 weeks after the endpoint assessment to assess successful tapering of study medication.

6.D.7. Three Month Follow-up Visits (Visit 19): Subjects will be asked to return at 3 months after the acute 16 week treatment phase is ended, to assess the enduring effects of medication treatment. They will complete TLFB, measures of mood, quality of life, alcohol use disorder symptoms, health symptoms, and blood will be drawn for biomarkers of alcohol use.

6.E. Study Treatments:

6.E.1. Pharmacotherapy Conditions. The medication will be administered as described above. Subjects who have unacceptable side effects or severe psychological symptoms (e.g., suicidal thoughts strong enough to suggest the subject can't be managed safely in the outpatient setting) will be withdrawn from the study.

Subjects will also be withdrawn from the study if they opt to discontinue it, become pregnant, or violate study rules (e.g., fail to attend two consecutive visits).

6.E.3. Medical Management (MM): This is a manual-based minimal behavioral psychosocial intervention that has been used effectively in previous clinical trials to optimize adherence to medication and treatment goals (12, 68). MM helps patients stay focused on treatment goals and on taking the medication, and will take about 20 minutes per appointment, at each appointment. This intervention will help reinforce treatment goals, and allow for a therapeutic interaction with patients on placebo. MM does not include more intensive therapeutic techniques such as those used in Cognitive Behavioral Therapy (CBT). The use of MM will facilitate the evaluation of the medication effect. We will use a modified version that allows for subjects to have a goal of abstinence or non-hazardous drinking.

6E.4.. Ensuring Adherence to MM Content and Procedures: To ensure that the MM is not confounded by variation in its administration, some of the treatment sessions (approximately 10%) will be audiotaped and, using materials adapted from the COMBINE Study, will be reviewed in an ongoing way to evaluate continued adherence to the MM format and content. A monitoring schedule will be created in attempt to review one session from each subject and review each of the different sessions equally. A rater will initially review the tapes with a checklist to ensure that the required elements of MM were covered during the session. An investigator will then review 20% of the initially reviewed sessions using the same checklist as above. The primary reviewer will also meet with the practitioners on regularly to discuss adherence to the protocol and any other related issues. If non-adherence to the protocol is identified, remedial training will be provided.

6.E.5.. Other Treatments Allowed During the Study: Subjects will be allowed to continue to receive, or will be referred for, additional psychiatric care as needed. This is similar to what has been done in previous studies in this population. They can receive antidepressants and other medications, as long as the medication is not on the list of those excluded. The type and amount of services received will be collected as data. Subjects will be allowed to participate in twelve step programs, group psychotherapy, day treatment programs etc.

6.F. Study Assessments: It is important to include measures from different sources to maximize validity. These include subject self-report, clinician ratings, and confirmation with laboratory data (i.e., GGT).

Study data will be collected and managed using REDCap electronic data capture tools hosted at VA CT Healthcare System. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources (72). In the event that REDCap is not working, assessments will be completed on pen and paper and entered into the database after.

6.F.1. Laboratory/Medical Assessments. The purposes of these assessments are: 1) to screen subjects for medical exclusion criteria, 2) to monitor medication adherence (retrospectively), 3) to assess potential side effects of medication, and 4) as objective measures of drinking. Prior to entrance into the study, each subject will receive a physical examination, urinalysis and urine toxicology, urine Ethyl glucuronide, CBC, and a chemistry panel (which includes electrolytes, liver enzymes, bilirubin, creatinine, and BUN). Women of childbearing potential will undergo serum pregnancy testing prior to beginning treatment and then urine pregnancy testing monthly thereafter (i.e., every 4 weeks) to identify women who become pregnant, so as to avoid exposing the fetus to the study medication. After 4 weeks on medication, and at the study midpoint (after treatment week 8) and at the end of the 16-week treatment phase, serum chemistry (including bicarbonate level), liver function tests, CBC, and serum GGT will be repeated. In order to monitor possible medication side effects, weight and vital signs (blood pressure and pulse) will be obtained at each treatment visit. Urine drug screens will be obtained at the initiation of the study to identify individuals who use drugs regularly, and will be repeated weekly thereafter. General metabolic and hematologic labs will be drawn more frequently if needed in order to monitor the health of subjects during the study. We will obtain blood phosphatydilethanol (PEth) levels at baseline, and weeks 8, 12 and 16 and urine Ethyl Glucuronide (EtG) levels at screening and weeks 4, 8, 12, 16, to use as biomarkers of alcohol use.

Table 2: Schedule of Assessments (See Table 3 for Stress Lab Assessments)

			Study Week																	
	SC	**BL**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**18**	**28**
Surveys/Procedures																				
Overview and Consent	x																			
Demographics	x																			
Locator Information	x																			
SCID-IV	x																			
Medical History/ Physical/Psych Exam	x																			
AUQ		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
BDI		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CIWA	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C-SSRS		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PCL-5		x	x	x	x	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	x	x	x	x
STAI		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
TLFB/measures of treatment received	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MM		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
IVR Daily Reports			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
AADUD	x																	x		x
CAPS-5		x								x								x		x
CGI-I						x				x				x				x	x	
CGI-S		x																		x
Q-LES-Q		x																x	x	x
RAND (SF-36)		x																x	x	x
SCID Section E																		x		x
SCID-II (antisocial)		x																		
SIP		x																x	x	x
TIPI		x																		
Early Termination Form																		x		
Endpoint Rating Form																		x		
Med-Q																		x		
Laboratory/Medical																				
Screening/Monitoring Labs	x					x				x								x		
DNA		x																		
PEth		x								x				x				x		
ETG (urine)	x					x				x				x				x		
Urine pregnancy test		x				x				x				x				x		x
Breathalyzer/Vitals/Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine drug screen	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: SC: screening; BL: baseline; SCID-IV: Structured Clinical Interview for DSM-IV; AUQ: alcohol urge questionnaire; BDI: Beck Depression Inventory; CIWA: Clinical Institute Withdrawal Assessement; C-SSRS: Columbia Suicide Severity Rating Scale; PCL-5: PTSD Checklist for DSM-V; STAI: Spielberger State-Trait Anxiety Inventory; TLFB: Timeline Follow-back; MM: medical management; CAPS-5: Clinician Administered PTSD Scale for DSM-V; CGI: clinical global impression; Q-LES-Q: Quality of Life and Enjoyment Satisfaction Survey; SIP: Short Inventory of Problems; Med-Q: medication questionnaire; TIPI: Ten-Item Personality Inventory

6.F.2. Psychological/Behavioral Assessments. The assessments listed below were chosen to provide standard, widely used measures to maximize comparability of findings with other studies in AD.

(a). Areas Assessed Only At Intake:

Sociodemographic/general patient information/Locator information. A demographic Interview will be used to gather data on medical history, socioeconomic and marital status, educational and occupational information, and history of the use of treatment services. Selection of follow-up locators is particularly important for locating patients in the event of an alcoholic relapse. At the time of enrollment in the study, patients are asked to nominate locators on the basis of relationship to the patient, duration of relationship (i.e., number of years known), current status of the relationship, and willingness to participate.

Psychiatric diagnosis. The Structured Clinical Interview for DSM-IV (SCID-I) will be used to classify patients according to the presence or absence of standard psychiatric disorders (73).

(b). Areas Assessed At Intake And During Each Treatment Visit:

Alcohol use patterns. The Time-Line Follow-Back Assessment method (TLFB), (74) will be used to estimate current alcohol consumption and drinking at intake and also weekly during treatment. This interview procedure will provide quantity/frequency of alcohol consumption data for each day during the period prior to the interview. Data on cigarette smoking will also be obtained using the TLFB. The Clinical Global Impression scale (CGI) will be used to assess progress in treatment monthly. The Clinical Institute Withdrawal Assessment (CIWA-Ar) will be used to facilitate assessment of withdrawal, and decisions regarding appropriateness for study entry and continuation with respect to physical dependence will be made based on the judgment of study physicians.

Psychological symptoms. The Beck Depression Inventory is generally regarded as a sensitive, self-report measure of depressive symptoms, and will be administered at each treatment visit to provide a means to monitor symptoms clinically. The Spielberger State Anxiety Inventory will be used to measure anxiety symptoms weekly (75). Suicidal ideation will be assessed at each visit using the Columbia Suicide Severity Rating Scale (76). Subjects with any current symptoms of suicidal ideation will be assessed by a licensed study clinician (i.e., an M.D., or Ph.D. psychologist), and referred immediately for further treatment if necessary. Subjects deemed by study clinicians to be at too high a risk of suicide to be managed in the outpatient setting will be discontinued from the study and referred immediately for treatment. PTSD symptoms will be measured by the Clinician-Administered PTSD Scale for DSM-V (CAPS-5) and the PTSD Checklist for DSM-V (PCL(77)-5). CAPS-5 will be conducted at baseline, week 8, week 16, and follow-up; PCL-5 will be conducted at baseline, weeks 1-16 and follow-up.) (78)

Desire to drink. Desire to drink will be assessed at each treatment visit with the Alcohol Urge Questionnaire (AUQ), (79).

Medication administration and medication-related adverse events. In addition to regular monitoring of vital signs, subjective reports of side effects will be monitored weekly using a list of adverse effects that have previously been reported for ZNS. A commonly used form (SAFTEE) for assessing and tracking side effects, their severity (on a scale of 1-5), and resolution, will be implemented.

Measures of treatment received. At each treatment visit, patients will be asked to return the unused portion of study medication. Staff will record the number of contact hours patients have been exposed to any treatment outside of the study that is related to their drinking and any self-help group attendance.

(c). Areas Assessed At Intake And At Treatment Endpoint:

Alcohol-related problems. The Short Index of Problems (SIP), which measures alcohol-related problems in five domains, will be used to assess change in such problems reported by patients in this trial (80). The SIP has good internal consistency, good concurrent validity, and adequate stability. The RAND 36-Item Health Survey, a 36-item self-report measure of life functioning in various domains, will be completed at study baseline, endpoint, and follow-ups. The Quality of life enjoyment and satisfaction survey (Q-LES-Q) will be used to assess quality of life in subjects.

(d). Areas Assessed Only At Treatment Endpoint:

Endpoint rating form. This is to be completed by the research assistant when the patient leaves treatment, indicating the patient's level of functioning at termination, and to chronicle as specifically as possible the reasons for termination (i.e., dropout, symptomatic failure, failure to comply with treatment), other circumstances behind the decision to terminate treatment, and who made the decision to terminate the treatment (patient, therapist, physician).

Brief 30 day assessment of Alcohol Dependence Symptoms. Subjects will be asked about AD symptoms for the last 30 days of treatment to assess for remission from the diagnosis.

Assessment of tolerability, efficacy, and masking questionnaire. This is a five-page questionnaire that measures the subject's subjective evaluation of the efficacy and tolerability of the medication, provides an opportunity for feedback on the study, and evaluates the success of the medication blinding procedure.

(e). Areas Assessed daily:

1. Daily subjective measures assessed with IVR: We will use IVR to collect daily ratings of alcohol-related expectancies, craving, anxiety/tension, feelings of self-efficacy to reduce drinking, drinking, and medication usage. These are the same procedures used to examine genetic moderation of medication effects in the studies by Kranzler et al. (81)(82)(83). Patients will be trained to use the IVR with a wallet-sized, follow-along sheet detailing each question in the IVR phone call, including answer options as a guide; this will be given to patients to assist them with the first few IVR calls. A research assistant will monitor calls to ensure that they are made daily and that any problems and questions are addressed immediately (to enhance accuracy and adherence). Patients who fail to call in during the allotted time receive a computerized reminder call [which has been found to increase the response rate by nearly 10% (84). Patients are paid $2 for each telephone call completed and an additional $6 for each week in which they complete 6 or more calls (i.e., up to $20 per week for 16 weeks or a maximum of $320). The use of a modest incentive helped achieve a call completion rate of 81.6% in a study of NTX (82) and 83.5% in a study of topiramate (27).

2. Daily drinking diary: Every evening, as part of the daily diary measuring subjective measures and medication usage, patients will record their alcohol consumption. The patient will report the number of standard drinks of beer, wine, liquor and "other" category. To capture all drinking during the preceding 24-hour period, patients are asked to report separately drinking from yesterday (in total), and any drinking during the current day, up until the time of the IVR report. This will allow us to examine lagged associations (85, 86). The time of the calls (5-9 PM) was chosen to minimize the potential for patients to have begun drinking heavily prior to making the calls. Patients are taught to complete the telephone interview, which requires less than 5 minutes/day. Daily measures of alcohol consumption obtained via IVR will enable us to examine co-variation of anxiety and drinking behavior to test for moderator effects. The IVR system is run centrally from our outside contractor Telsage, but will be implemented at all three sites, and is HIPAA compliant and has been reviewed and approved by the SRO. Cellphones will be provided to subjects without a phone during the study.

3. Daily medication usage: Using IVR, patients will report daily their use of medication that day, which correlated highly (r=0.91) with electronic monitoring (i.e., MEMS cap) (87).

6.G. Exploratory DNA Sampling And Pharmacogenetic Analysis, Specific Aim 4:

We will use an inexpensive method for collecting, shipping, storing, purifying, and analyzing DNA samples with the Oragene saliva DNA sample kits. Saliva for DNA will be obtained at study baseline with informed consent using the Oragene kits. Genotyping for candidate markers will be carried out either in the CTNA affiliated Laboratory of Psychiatric Genetics located at the West Haven VA. DNA will be purified from saliva using sample preparation kits that are optimized for the Oragene samples, utilizing optimized spin column based extraction. The Oragene kits typically obtain ~110µg of high-quality DNA per 2ml of saliva obtained. TaqMan allelic discrimination assays are available for the polymorphisms of interest. Genotyping will be performed using the 5'-nuclease TaqMan closed-tube fluorescence method and an ABI 7500 Sequence Detector System for post-PCR plate reads.

Additionally, at the West Haven Site, we may use blood for DNA genotyping if resources become available to do so. These would also be stored at the CTNA affiliated Psychiatric Genetics Lab.

6.H. STRESS REACTIVITY LAB PROCEDURES (Specific Aim 5):

6.H.1. *Intake:* Qualified staff will meet with eligible subjects to explain all study procedures and risk/benefits and obtain informed consent. Next, scripts for the imagery procedures will be developed and audio recorded on the day of the lab, or after screening but before the day of the lab. The stress reactivity lab session is

performed twice; the first stress reactivity lab session occurs after screening but prior to starting medication. The second stress reactivity lab session occurs after being on the target dose for at least 2 weeks (i.e. between weeks 9-16) Each stress reactivity lab takes place on one day, and is approximately 3 hours long. A description of the procedure is provided in Table 3.

6.H.2. *Imagery Script Development*: First, scripts for the guided imagery induction will be developed. The ***stress imagery script*** will be based on subjects' description of a recent personal stressful event that is self-rated as an 8 or above on a 10-point Likert scale, where 1 = "not at all stressful" and 10 = "the most stress I have recently felt in my life". Examples of acceptable stressful situations include breakup with significant other, a verbal argument with a significant other or family member or unemployment-related stress, such as being fired or laid off from work. A ***neutral-relaxing script*** will be developed from the subjects' commonly experienced neutral-relaxing situations. Neutral-relaxing events that involve nicotine or alcohol/drugs will not be allowed. An ***alcohol craving cue imagery script*** will be based on subjects' description of a recent event in which alcohol was consumed. Stressful situations will not be acceptable for these latter two types of scripts.

A 'script' or description of each situation will be developed using Scene Development Questionnaires which obtain specific stimulus and response details, including specific physical and interpersonal context details, verbal/cognitive attributions regarding the people involved, and physiological and bodily sensations experienced for the situation being described. The three scripts for each subject will then be recorded on an audiotape (or similar technology) for guided imagery in the laboratory sessions. The order of stress, alcohol-cue, and neutral scripts will be assigned randomly, and counterbalanced across subjects. prior to the first stress lab. Detailed procedures are outlined in the imagery development procedures manual (88).

6.H.3. ***Manipulation Check for Script Development*****:** All three scripts will be rated on a Likert scale from 1 to 10 on a standard rating form (Independent Rating Scale) by two objective independent raters for stressful and emotional content. If a script scores below a rating of 8 for stressful content on a five-point rating scale the subject will be asked to develop a new script prior to the laboratory sessions. These procedures ensure that the stress scripts of all subjects are equated in intensity and content. It further ensures that differences in stress reactivity are not due to differences in intensity and emotional content of the stressor. The procedures for development of imagery scripts, rating of scripts for content and physiological activation are similar to those used by Miller et al. (89)and have been successfully used in previous work by co-investigators.

6.H.4. ***Imagery & Relaxation Training:*** subjects will be introduced to all self-report measures and instructed how to complete them. In order to minimize baseline imagery variability participant will be given relaxation and imagery training, as described in the imagery training procedures manual (88). Relaxation training will be approximately 20 minutes and will consist of progressive muscle relaxation technique. The imagery training will consist of two types of visualizations. First, participants will be asked to visualize an unemotional scene, such as reading a magazine. Second, they will be presented with an unemotional but physically arousing scene, such as exercising in a gym. Here, the emphasis will be placed on assuring that participants are aware of physiological changes, increased heart rate, or breathing. Subjects will be given instructions throughout the imagery exercises regarding the process of imagining the scenes and maintaining the visualization for an extended period of time.

The order and content of the imagery conditions will not be revealed to the subject or to the research staff conducting the sessions. ***The neutral script will always occur in between the stress script and alcohol-cue script, the both of which will be randomized to occur before or after the neutral script.*** In the imagery task, the subjects will be asked to imagine the situation being described vividly, 'as if' he/she is in the specific situation, until asked to stop. The imagery script will be played to the subject over headphones and the subject will be required to imagine the situation for 5 minutes.

After the imagery period, relaxation instructions will be provided to ameliorate any residual effects of imagining stressful situations. In addition to reducing anxiety, relaxation instructions have been found to be effective in reducing alcohol cue-induced craving in the laboratory (88)(90). Following the scheduled assessments, subjects will remain on the unit until subjective and physiological measures return to baseline levels. Subjects will continue to be supervised by a psychologist or psychiatrist until they feel safe. Should subjects experience adverse psychological reactions to the procedure, immediate counseling and relaxation instructions will be provided. More severe reactions will be addressed pharmacologically by one of the study physicians. Long-term psychological effects are not expected because similar trauma exposure procedures are used in empirically-

validated therapies for PTSD.

6.H.5. Lab Session: After arrival on the research unit and before the start of the first laboratory session subjects will be instructed to relax for a few minutes by clearing their minds and focusing on deep breathing. Subjects will be instructed that when situation is being read to them, they should try and imagine as though they are in the situation, and as though it is happening at that time. They will be asked to imagine themselves in the situation until they are asked to stop. The experimental procedure will follow the same format for each of the three conditions consisting of baseline relaxation, imaging scripts and recovery period for 10 min.

TABLE 3 Schedule for Stress Reactivity Laboratory Session (all times are approximate)

T -20	Subject arrives; BrAC check (< 0.02), urine tox screen, CIWA, psychophysiological setup; BART, BIS, STAI, brief 10 minute relaxation
Stress script, or Alcohol Cue script, (Script #1)	
T 0	Baseline, BP & HR recording, Craving and emotion ratings (VASA, VASC, DES-R, AUQ, PANAS, STAI-6)
T +10	Image period (administration), BP & HR recording,
T +15	Craving & emotion ratings, BP & HR recording
T +25	Recovery period, BP & HR recording,
T +30	Craving & emotion ratings, BP & HR recording,
T +40	10 minutes relaxation period
Neutral script (Script #2)	
T +50	Schedule of measurements same as above for Script #1
Stress, or Alcohol Cue script, (Script #3)	
T +100	Schedule of measurements same as above for Script #1
T + 150	Craving and emotion ratings; Subject assessed and cleared by study staff

Abbreviations: HR/BP: Heart rate/Blood pressure, BrAC: Breath Alcohol Concentration; VASA: Visual Analog Scale for Anxiety; DES-R: Differential Emotions Scale-Revised short form; POMS: Profile of Mood States; AUQ: Alcohol Urge Questionnaire; PANAS: Positive and Negative Affect Schedule: BIS: Barrett Impulsivity Scale; BART: Balloon Analog Risk Task. STAI: State-Trait Anxiety Inventory.

6.H.6. Outcome Measures For The Stress Reactivity Lab:
Positive and Negative Affect Schedule (PANAS): PANAS is a 20-item scale that assesses both negative and positive affective states (91). Subjects rate adjectives describing affective states on a scale of 1 to 5 using a specified time period (e.g., now, today, past week etc.). Scores are then added up to generate negative and positive scale scores. This scale is short, easy to administer and has good psychometric properties.

Visual Analog Scale - Anxiety (VASA). Anxiety levels will be measured using a self-report VASA. Participants will be asked to rate their level of anxiety, how “anxious, tense and/or jittery” they feel at that particular moment. Their responses can range from 0=”not at all” to 10=”extremely high”.
Visual Analog Scale - Craving (VASC). Current craving for alcohol will be measured using a self-report VASA. Participants will be asked to rate their level of craving, “desire for a drink” they feel at that particular moment. Their responses can range from 0=”not at all” to 10=”extremely high”.

The Differential Emotions Scale-Revised short form (DES-R)(96) will be used as a measure of subjective emotional experience. The measure consists of a number of subscale and for the present study we will use five subscales: sadness, anger, joy, fear, and anxiety. Each subscale is made up of 5 adjectives describing the particular emotion state. Participants rate on a 5-point scale the extent to which each word describes how they

feel at the present moment. The DES shows good psychometric properties (96). The DES has been used to examine subjective emotion following laboratory mood inductions (90).

Alcohol Urge Questionnaire (AUQ) will be used to assess subjective craving for alcohol at each timepoint (79).

Impulsivity will be assessed through the Balloon Analogue Risk Task (BART) (70) and Barrett Impulsivity Scale (BIS) (71). The Go/No-Go Task will assess the ability to withhold responses to an infrequently occurring target (No-Go trials). A series of blue and green rectangular shapes are presented every 1150 ms and participants are instructed to press a spacebar every time the green rectangular shape appeared, and to give equal importance to speed and accuracy. The primary outcome is the number of errors on the No-Go trials (97, 98).

State-Trait Anxiety Inventory (STAI) will be used to assess anxiety symptoms; the full version will be used at the start of the lab session and the shorter version (STAI-6) will be used for all other indicated timepoints (75).

6.H.7. <u>Physiological Measures:</u> BP and HR will be assessed using an SD-700 monitor.

6.I. Statistical Plan and Power Analysis:

6.I.1. Procedures: Procedures for the monitoring and analysis of data were developed during previous clinical trials conducted in the VAARC and CTNA and will be overseen by Dr. Ralevski.

6.I.2.To Examine The Effectiveness Of ZNS (Specific Aim 1, Primary Outcome):

We will use the percentage of subjects with no heavy drinking days (**PSNHDD**) as the primary outcome variable. This outcome is the FDA recommended endpoint for pivotal trials, and is described in Falk et al., (2010). The PSNHDD can be derived from each subject's TLFB data. An important initial consideration in considering effectiveness will be to identify baseline differences between groups that may have occurred despite randomization. **Successful outcomes during the treatment trial will be defined in terms of a statistically significant difference on the primary outcome measure: PSNHDD, compared during the 8 weeks of active treatment at the target dose, allowing for a 6 week grace period for the medication titration.** For all analyses, heavy drinking days will be defined as follows; for men > 5 drinks in a day and for women > 4 drinks in a day. Patients will be followed irrespective of whether they continue to receive medication treatment, so that analysis will include all data available for the 8-week treatment period. The analysis will be **intent-to-treat**, and dropouts will be considered as having relapsed to heavy drinking. We will use a logistic regression analysis with PSNHDD as a categorical dependent variable. Medication condition (placebo or ZNS) will be the main independent variable, and we will include the variables of early onset of alcoholism (EOA, binary), and the use of additional psychotropics (e.g., antidepressants, a binary variable) as covariates. The α will be set at .05 for the primary outcome variable. Between site differences will be explored.

We will use a mixed models approach to examine **secondary outcome measures (Specific Aim 2**) for a statistically significant difference in; drinks per week, and heavy drinking days per week, the outcomes used in the pilot study. The model will include fixed effects for medication group, week, and the interaction between medication and week, also controlling for pre-treatment drinking behavior data, and using a random effect for intercept. We will incorporate a grace period corresponding to the time it takes to titrate the medication to target dose into the models, and we will focus the primary analysis on the 8 weeks of treatment at the target dose. Aggregate outcome measures such as the percentage of heavy drinking days, which can be examined using several different methods, will be considered. A statistically significant difference on any of the secondary measures of both heavy drinking and drinking, with clinically significant effect sizes, will be considered a relative success for the medication. Additional secondary outcome measures will include changes in GGT level, measures of alcohol urge or craving to use (AUQ), measures of depression and anxiety, measures of physical health and quality of life (Q-LES-Q, the and the RAND-36) and level of alcohol-related problems (as measured on the SIP). These can also be performed with the mixed models approach. Statistical models evaluating time to relapse, drinking trajectories, percentage of abstinent days, drinks per drinking day, and total abstinence rates will be considered. **We will use the Bonferroni correction for the secondary outcomes and additional comparisons to guard against chance findings.**

All secondary outcome analyses will be by intention to treat, a conservative approach that is aimed at avoiding an overestimation of the treatment effect and will include all subjects that take any medication and provide drinking data for at least one week. The use of multilevel repeated measure statistical models may increase the study power and potential to detect a treatment effect. This type of repeated-measures analysis 1) provides missing-data imputation procedures that are both conservative and logical; 2) allows for the measurement of the exact time that a given patient is measured at baseline and follow-up points, which need not be the same among patients; 3) plots and analyzes linear and non-linear time-course functions both overall and for subgroups of patients based on each patient's best estimate linear and non-linear regression line plots. We will use all available data on individuals and thus dropouts provide data until the point of dropout. The best-fitting variance-covariance structure between the repeated measures will be selected based on Schwartz-Bayesian Information Criterion (BIC). We will compare dropout patterns between groups and if there are concerns of informative dropout and/or informative intermittent missing data, we will use pattern mixture models (Hedeker and Gibbons, 1997) to perform sensitivity analyses to our main analyses. Adherence to the medication will be evaluated and factored into the analysis. We will evaluate and compare both medication conditions (placebo, ZNS) for percentage of prescribed pills taken. We do not expect a difference, but if one is found, we can then perform additional analysis on the main outcome variables to estimate treatment effects adjusted for percent pills taken. The number of MM sessions attended will be recorded and analyzed similar to the medication adherence.

The three-month follow up data will be gathered using a retrospective TLFB at the follow-up time point, and will be analyzed using logistic regression for PSNHDD, and either linear mixed models or Hierarchical Linear Modeling (HLM) for other outcomes. We will examine that drinking data between the end of treatment and the three-month time point and use the same outcomes as the main analysis. We will be able to examine for persistent effects of ZNS on drinking behavior and related outcomes. These analyses will include pre-treatment and within-treatment drinking data as covariates to evaluate the post-treatment effects of ZNS.

6.I.3. To examine the tolerability of ZNS compared to placebo (Specific Aim 2): An important consideration in evaluating the outcome of this pilot study is the tolerability of ZNS in subjects. To examine tolerability in the present study, the frequency of specific groups of adverse effects of a moderate-to-severe nature will be tabulated and compared to placebo using Fisher's Exact Test. We will also compare ZNS and placebo groups on the number of subjects for whom medication treatment is discontinued due to adverse effects. Overall dropout rates will be examined, as well as measures of medication adherence.

6.I.4. To use telephone-based daily process data collection to elucidate the mechanism of action of ZNS as it relates to changes in craving, anxiety, self-efficacy, and genetic variation (Specific Aims 3, 4): Multilevel models will be used to evaluate the associations between craving, self-efficacy, anxiety, and daily drinking and how these associations vary as a function of medication group and GRPS. Similar to Kranzler et al. (82), we will focus on predicting nighttime drinking (i.e., drinks consumed after the early evening report), but here we will use psychological measures reported during the early evening in the daily survey. Nighttime drinking levels will be determined by subtracting the number of drinks consumed during the current day from the total number of drinks consumed for that day (reported the following day). We will follow the general analysis scheme used by Kranzler et al. (82), but will use mixed effects/multilevel models, rather than generalized estimating equations (GEE) models (99) because mixed models give unbiased estimates under less restrictive assumptions about missing data. We will examine the number of drinks consumed (using a Poisson model or negative binomial model if there is overdispersion). We will use the HGLM module of the HLM7 program, as it is more flexible for some of our models than PROC GLIMMIX in SAS. Analysis will focus on the last eight weeks of treatment, consistent with the analyses of outcomes in Aim 1. We will test the hypothesis that ZNS reduces nighttime drinking and that craving, anxiety, and GRPS act as moderators of this effect. We anticipate greater ZNS effect in subjects with greater anxiety, craving and genetic loading (greater GPRS). We will examine whether ZNS's effect on drinking is mediated by self-efficacy using the approach of Kraemer et al. (100, 101), such that self-efficacy is significantly affected by ZNS treatment, and has a main or interaction effect on nighttime drinking in the model containing both treatment and the potential mediator as predictors.

6.I.5. Stress Reactivity Lab (Specific Aim 5): We will compare pre- and post-treatment changes in levels of anxiety, craving, and impulsivity measures induced by stressful and alcohol-cue imagery in the lab. We will test if the mean induced changes are attenuated by ZNS more than placebo using ANCOVA. The amount of reactivity pre-treatment will be explored as a covariate in secondary outcome models.

6.I.6. Sample Size And Power Estimate (Specific Aims 1-3):
For the primary outcome PSNHDD: Based on the trend in the pilot study favoring ZNS with 12 subjects in the ZNS group without relapse to heavy drinking, and only 7 in the placebo group, we estimated the power with the previously planned sample size. Based on these proportions, we should be well powered (>89%) to detect a difference in PSNHDD with 80 in each group. Since dropouts will be counted as relapsed to heavy drinking, we will still be powered at that level, regardless of the number of dropouts. Even in the event that we don't recruit as many subjects as expected (e.g., N=64 in each group, approximately) we estimate the estimated power will be about 76% to detect a difference between the medication and placebo.

For secondary outcomes: Based on the effect sizes from our pilot study of ZNS (showing a small effect size on heavy drinking and a moderate effect size on total drinking), we estimated that a study with **N=160** (subjects would be well powered (>.98) to detect a significant difference on the secondary outcomes heavy drinking days per week, and total drinks per week. In our pilot study we ran a linear mixed models and found a decrease in drinking of 1.4 drinks per week for the controls versus 2.2 drinks per week for ZNS. The variance in the decrease in drinking (slope) was approximately 0.9. Assuming similar results, a Monte Carlo simulation in Mplus showed that with a sample of 160 subjects evenly split between groups and measured weekly over 12 weeks there is power of 0.98 to detect a significant difference in slopes between groups. Also, in our pilot study we found a decrease in heavy drinking days per week of 0.2 for the controls versus 0.3 for ZNS. The variance in the decrease in drinking (slope) was about 0.1. Assuming similar results, a Monte Carlo simulation in Mplus showed that with a sample of 160 subjects evenly split between groups and measured weekly over 12 weeks there is power of 0.99 to detect a significant difference in slopes between groups. **Even if dropouts reached 40%, we will be well powered (>.80)** for detecting differences on **secondary outcomes.**

6.I.7. Pharmacogenetic Data Analyses and Power Estimate (Exploratory Specific Aim 4): We will explore the interaction of the DBH SNP and ZNS described in section B.3.e, in terms of treatment response using mixed models or logistic regression where appropriate. With an N=160 we should be well powered to detect an effect of the DBH SNP, based on our previous study, from which we calculated an OR of approximately 12.6 for those on naltrexone with the advantageous allele (Cohen's d = 1.4). Given the large effect size observed, albeit from one small study, we should be well powered (> .99) to find a significant pharmacogenetic interaction if it exists on PSNHDD or secondary outcomes. Using the more conservative effect size from the Wald chi square logistic regression model for the DBH genotype-naltrexone interaction, (Cohen's d = .5), we should be well powered (>.99) to find a similar interaction for ZNS. Given the exploratory nature of the pharmacogenetic analyses, they will not be corrected for multiple comparisons. Estimates of effect sizes will be used for replication of the findings in appropriately powered future studies.

6.J. Timeline For Recruitment And Other Study Objectives: As shown in Table 4, recruitment will take place over 45 months, requiring enrollment of approximately 40 total patients per year (or approximately 2 patients/month at each site).

Table 4: Timeline of Performance Goals

Activity	Year 1				Year 2				Year 3				Year 4				Year 5			
Staff training & study preparation																				
Patient enrollment																				
Endpoint assessments																				
3-month follow-ups																				
Data entry & cleaning																				
Data analysis																				
Report writing																				

6.K. Plan For Managing And Integrating The Two Clinical Sites: This project will take place at two sites: the West Haven VAMC (VA Connecticut Health System) and the Bedford VAMC (both of which are in VISN1). The principal investigator (Albert Arias, M.D.) and Bedford site investigator (Nitigna Desai, M.D.) have agreed to engage in this collaborative effort, each bringing expertise in alcohol research that will be synergistic. Working together, the partnering sites will operate via a steering committee that will ensure the integrity of the research plan with an emphasis on safety, adherence to the protocol, and the integrity of the data and its analysis. The researchers will build upon the existing relationship between the investigative groups that has resulted in a successful collaboration for more than ten years.

The steering committee will consist of the PI and site investigator (Dr. Arias and Dr. Desai), as well as Dr. Petrakis, Dr. Ralevski, a project coordinator from each site, and an administrative coordinator for the total project. This team will work closely together to maintain scientific integrity through proper protocol implementation, attention to subject recruitment/retention efforts, and appropriate reporting to the regulatory bodies (e.g., the Data and Safety Monitoring Board). At each site, Drs. Arias and Desai will conduct weekly meetings with their respective research teams in which clinical and administrative issues will be reviewed and discussed. There will be monthly video-teleconference call meetings for the steering committee to discuss the study's progress and any issues that arise. Both sites have readily available video-conferencing and telephone conferencing equipment available to them through the VA. Drs. Arias, Desai, Ralevski and Petrakis will also be in telephone and email contact as needed. Dr. Arias will perform a one-day site visit at the Bedford VA twice yearly, and more frequently during start up as it is within driving distance.

6.K.1. Data management, integration, and integrity between sites*:* Drs. Arias and Ralevski, and the administrative coordinator, will oversee the data management and transfer of data from the Bedford VAMC site to the West Haven VAMC site where it will be stored, analyzed, and eventually disseminated. Secure Internet portals for transfer of research data are available from the VA and will be used to transfer information between sites, though the data is actually de-identified before being sent. Data at the Bedford site is collected using tele-forms that can be electronically scanned (and automatically) entered into SPSS files by staff at Bedford. This electronic form scanning is already in place and has been used in previous collaborative efforts. The forms were designed and generated at West Haven, and sent to Bedford. We already have all the necessary forms developed that would be needed for this study. The use of the scanned forms reduces data entry errors and eliminates the need for manual cleaning. The data is de-identified on site, and the resultant files sent periodically to the West Haven research staff where it is joined with the West Haven data and stored in the Alcohol Research Group's computer system. Drs. Ralevski and Arias will oversee this via weekly communication with the Bedford site staff. The data entry process will be observed and reviewed at the Bedford site by Dr. Arias at periodic visits. Dr. Ralevski will be in charge of the master database.

7. Limitations and/or potential pitfalls:

Pitfalls, Alternative, And Future Plans:

We anticipate that subject recruitment and collaboration between the two research sites will continue to go smoothly with this study, as it has with those in the past. One potential pitfall is that the long titration period for ZNS may detract from the medication effect or influence retention. To deal with this possibility, we have shortened the titration period by several weeks compared to the pilot study. Another potential pitfall is that the inclusion of subjects with some degree of heterogeneity in terms of co-occurring disorders (i.e., those with just AD, as well as those with AD and a history of major depressive disorder, or sub-syndromal PTSD, etc.) could make the findings difficult to interpret. We will however gain the benefit of generalizability if the medication proves effective in this population. We will likely be able to statistically control for many of these factors. Allowing subjects to receive other mental health treatments during the study could similarly cause interference, but adds to the generalizability of results.

We anticipate that, similar to recent findings with other medications to treat alcoholism, the results of the exploratory analysis of pharmacogenetic and other moderators of treatment will yield interesting results that will transform our understanding of the main analysis. This is an exciting future direction, and the study results may help to identify predictors of preferential response to ZNS, and may help us to personalize treatment for veterans in the near future. Even if we find that the age of onset of alcoholism is the most important predictor of

response to the medication, and that genotype does not matter, that will be very useful information that can be applied clinically. Anticonvulsants are a useful class of medications in alcoholism treatment, and further study of this class of medication (and especially ZNS) is warranted. Further knowledge of ZNS and its effects in alcoholism treatment, combined with ongoing research on similar medications with notable differences (such as topiramate) will facilitate a deeper understanding of the mechanism of action of drugs to treat alcoholism, and will have positive effects on drug development.

8. HUMAN SUBJECTS PROTECTION:

RISKS TO HUMAN SUBJECTS:

8.A. HUMAN SUBJECTS INVOLVEMENT AND CHARACTERISTICS:

Zonisamide (ZNS) Effectiveness Trial and Pharmacogenetic Analysis: Outpatient heavy drinkers with *alcohol dependence (N=160 male and female veterans*) who are identified through screening, referrals, and flyers posted at VA facilities will participate in this study. Patients must be heavy drinkers (aged 21-70) who are motivated either for abstinence from alcohol, or to reduce their drinking to non-hazardous levels. All patients will undergo careful medical and psychiatric assessment and must meet all inclusion and no exclusion criteria (as described in the Methods section) to qualify for this study. The patients will all be adults in good physical health who have capacity to provide informed consent. Based on our experience with outpatient recruitment of veterans, we anticipate that approximately <5% of subjects will be female, which is proportional to the percentage of female respondents to the advertisements we employ with veterans. Subjects will be randomized to zonisamide or placebo groups and return weekly for assessment and medication management. This is a 16-week randomized, double blind, placebo-controlled, clinical trial to evaluate the effectiveness of zonisamide for alcohol dependence in a representative sample of veterans. Recruitment and methods will be similar at both study sites. There is a longstanding record of successful research collaboration between the Bedford and West Haven sites, and adequate infrastructure exists to ensure subject safety and confidentiality. Teleconferencing equipment is available at both sites to facilitate meetings and cohesiveness of the research team.

Research Material: Research material will include information and DNA obtained from patients. Other data will be obtained by physical examination, clinical laboratory evaluation (including genotypes), and data from observation of patients by study staff. All data will be obtained exclusively for research purposes and will be at no cost to the patients. They will be paid a nominal but fair amount of money for their time and participation, up to *$1045* (i.e., enough money to fairly compensate and encourage follow-up without being coercive or encouraging risk taking). The payment schedule is outlined in detail below (SEE TABLE 5). Additionally, subjects that travel more than 10 miles from home to come to study visits will be paid an additional $15 dollars per visit to ensure proper compensation for gas, and travel time.

Additionally, participants can earn up to $320 for completing the IVR phone calls ($2 per completed phone call plus $6 for each week where 6 or more calls are completed (up to $20/week for 16 weeks)). If they do not have a cell phone to complete the calls we will give them one to borrow during the study which must be returned when they complete the study.

By participating in the stress labs, subjects can also earn $40 for the script development, $100 for each of the two stress labs ($200 total), and up to $40 for the computer tasks during the stress labs (up to $20 per lab session).

If all parts of this study are completed, participants have the potential to earn up to $1645 (this does not include the additional travel compensation mentioned earlier). This payment is for the time and effort associated with study assessments and procedures.

The alcohol clinical trials unit staff at both the West Haven VAMC and the Bedford site have considerable experience in administering questionnaires and diagnostic assessments, as well as with protecting that data appropriately.

Payments for screening, outpatient visits and follow up will be made through electronic funds transfer (EFT). Participants will need to provide us with your banking information by completing a special payment form. Alternatively, if participants do not have a bank account, a check will be mailed to them instead. This check(s) will be mailed to the address they provide us with. Alternatively, patients may choose to receive gift certificates issued to them for use at the VCS canteen (retail store) or VCS cafeteria here at the VACHS. Study payments are subject to withholding for outstanding federal debts (i.e., defaulted student loans, interstate child support, back taxes etc) without notification.

Payment for participation in IVR phone calls and Stress labs *will be given in the form of cash at the time of the subjects participation.*

TABLE 5: Subject visit and payment overview:

Visit title	**Visit #**	**Weeks completed on medication**	**Payment (US $)**
Screening	0	0	50
Baseline (start meds)	1	0	65
Regular visit (1 week after last)	2	1	50
Regular visit (1 week after last)	3	2	50
Regular visit (1 week after last)	4	3	50
Regular visit (1 week after last)	5	4	50
Regular visit (1 week after last)	6	5	50
Regular visit (1 week after last)	7	6	50
TARGET dose 500mg (regular weekly visit, 1 week after last))	8	7	50
Regular visit (1 week after last)	9	8	60
Regular visit (1 week after last)	10	9	50
Regular visit (1 week after last)	11	10	50
Regular visit (1 week after last)	12	11	50
Regular visit (1 week after last)	13	12	50
Regular visit (1 week after last)	14	13	50
Regular visit (1 week after last)	15	14	50
Regular visit (1 week after last)	16	15	50
Endpoint visit (1 week after last visit start taper)	17	16	60
Two weeks post endpoint visit follow up	18	18 (taper)	50
3 month follow up	19	NA	60
TOTALS	**20 (including screening)**	**18 weeks on med**	**1045**
Additional Compensation			
Stress Script Session			$40
Stress Lab 1			$100
Stress Lab 2			$100
Computer Tasks			Up to $40
IVR Phone Calls			Up to $320

Maximum total for all visits, labs, and phone calls			**$1645**

These subjects (all veterans) are recruited from the community as described above, and have been diagnosed with *alcohol dependence*, and screened through all the inclusion and exclusion criteria, Information will be gathered using forms and other means of collection as described in the methods section. The TLFB, AUQ, SCID, and similar questionnaires (as described in the methods section) will be collected and stored in a folder for each subject, with all data being coded and secured as per IRB requirement. Blood and urine samples for the study are stored securely and coded with a subject number only. Clinically relevant material will be stored in the Federal VA's electronic medical record (which is heavily protected and secured) and will facilitate care and safety at both project sites.

8.B. POTENTIAL RISKS TO SUBJECTS AND PROCEDURES TO MINIMIZE POTENTIAL RISKS:

There are several classes of potential risk to patients enrolled in this study:

General Procedures: There is some risk that patients will be identified as participants in a study of treatment for heavy drinking or that the clinical assessments will adversely affect patients' well-being.

Counseling: This Medical Management (MM) treatment has been used safely with alcohol-dependent patients in the COMBINE Study. Psychological risks are minimal and not different from those of equivalent non-study treatments.

Collection of DNA: Biological materials from individuals are identified by code number rather than by name after saliva is collected for DNA studies. To eliminate the potential risk of confidential health information being leaked or stolen, all samples and accompanying phenotypic data will be de-identified after study completion, making it impossible to link any genotypic or phenotypic data to a particular person. No genotype data are released to subjects under any circumstances. A heavily secured link between the genetics sample codes and clinical trial data will exist until study completion to ensure data integrity, but the data set will be subsequently de-identified.

***Medication**:* Fatigue was the only common adverse event that occurred significantly more frequently with zonisamide than with an inactive placebo in a treatment trial aimed at weight loss in obese patients for weight loss (Gadde et al. 2003). In our recently completed pilot study of zonisamide for alcohol dependence, only gastrointestinal adverse events were reported significantly more than placebo, and there were no serious AE's. There were no observed problems with medication and alcohol interactions that seemed to be deleterious. In trials of subjects with bipolar disorder and epilepsy, more severe adverse reactions have been reported, although the most serious psychiatric adverse events seem to be limited mostly to the epilepsy population. Suicidal ideation and mood changes (depression, mania) are rare but possible reactions to the medications, so all subjects will be monitored for these potential adverse events closely.

Overall, the safety profile of zonisamide in the treatment of epilepsy, where zonisamide was added to another agent (such as carbemazepine), shows that it is generally well tolerated but with some common mild side effects and rare serious adverse events reported. The most common adverse events observed in these studies that were more common than placebo were: somnolence (17% vs. 7%), anorexia (13% vs. 6%), dizziness (13% vs. 7%), headache (10% vs. 8%), nausea (9% vs. 6%), and agitation/irritability (9% vs. 4%). Psychosis has been reported rarely, except in trials with seizure disorder patients, where the incidence was approximately 2%, but was likely related to their seizure pathology (Micromedex database). Renal calculi can also occur with zonisamide. There were no reports of psychosis in a trial of zonisamide for obesity. **In epilepsy trials, rare but**

potentially serious reactions that occurred more often than in placebo were hematologic reactions (INCLUDING APLASTIC ANEMIA AND AGRANULOCYTOSIS*)*, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Overdose of zonisamide can result in coma, bradycardia, hypotension, and respiratory depression. Additionally, the FDA has added a warning about the rare but serious occurrence of metabolic acidosis with zonisamide*.* IN ORDER TO SAFEGUARD AGAINST THESE RARE BUT SERIOUS ADVERSE EVENTS: we will monitor blood counts and serum bicarbonate levels at several time points throughout the study to identify changes in hematologic function or acid-base balance as early as possible. Subjects with a history of severe allergic reactions or autoimmune illness, sulfa drug or penicillin allergy, will be excluded from the study to reduce the risk of a severe allergic reaction to the medication. Suicidal ideation and mood changes can occur, so subjects will be monitored closely at their weekly visits using psychometric measures of mood and suicidal ideation. The Columbia Suicide Severity Rating Scale will be used routinely to help identify subjects in need of further evaluation or intervention.

Blood and Urine Collection. Blood chemistries and urinalysis are done at baseline primarily as safeguards to subjects and at subsequent time points for safety reasons and to validate self-reported alcohol consumption and medication adherence (retrospectively). Urine toxicology assessment is done to determine the extent of illicit drug use. These procedures should add no risks other than those normally associated with them (e.g., bruising at the site of venipuncture).

Rating Scales and Questionnaires. These are all non-invasive and should add no risk. The major disadvantage is the time taken to complete them and possible breach of confidentiality. Our past experience with these evaluations indicates they are acceptable to patients. Careful efforts to maintain confidentiality have been effective in previous research done at both sites.

8.C. ADEQUECY OF PROTECTION FROM RISKS:

Subject Recruitment And Consent Procedures:

Patients will be recruited using the following methods: through referrals to the West Haven VAMC alcohol clinical trials unit; by posting/distributing recruitment materials at VA facilities with public posting areas or other means of communicating with veterans, such as by posting/distributing recruitment materials in community settings with public posting areas or other means of providing community access to materials (such as hospitals, town halls, public libraries, YMCA, health fairs/organizations). Bus and newspaper advertising will also be used. We will use IRB-approved recruitment materials, which advertise for regular or daily drinkers who want to reduce or quit drinking. A partial waiver of consent and HIPAA Authorization will be obtained from the IRB to allow for preliminary phone screening for calls initiated by potential patients. Those individuals deemed eligible for in-person screening will sign a HIPAA Authorization and study consent form at their first visit. During the in-person screening visit (once telephone screening shows preliminary eligibility), each patient will receive an explanation of the study protocol, its risks, potential benefits, and alternative treatment by a study staff member. Following resolution of any questions, patients who appear to understand the nature of the study and consent will be asked to sign the study consent form. An entire copy of the informed consent form will be given to each patient. Based on our experience with this method of recruitment, we anticipate that about <5% of patients eligible and willing to participate will be female. Because we will be recruiting veterans from facilities throughout the Greater Hartford and New Haven area, including outreach to the minority communities in the area, we anticipate that approximately 25% of patients enrolled in the study will be African-American and 15% will be Latino. Children will not be included in the study sample. All subjects will be veterans.

Consent Procedures: After routine screening, all subjects will receive an explanation by the research nurse of the risks, benefits, treatments, and study procedures and options for alternative treatment. Following resolution of any questions, subjects are asked to sign the consent form, once there is a clear indication that the subjects understand the nature of the study and the consent.

Protection Against Risk To Subjects: Inclusion/exclusion criteria, and the use of experienced, well trained research assistants, psychologists, and research nurses in the initial screening helps to avoid the acceptance of subjects with insignificant alcohol use into the study. Careful medical and psychiatric evaluation minimizes the likelihood of including individuals with illness that contraindicates participation in the research. Repeated measurement of laboratory parameters will enable the early identification of subjects who might experience an adverse reaction that is not readily reported by the subject. Confidentiality in regard to collected materials is maintained via a numbered reference system maintained by the project director. Subjects' names appear only on a consent form and "key" form kept by the project director. Subjects are withdrawn from the study if they show severe clinical deterioration. Subjects who are removed from the study are referred to treatment at a local treatment facility (in this case most likely the corresponding VA), according to their needs and wishes. Additional safeguards are described in section 1.B above. Suicidal ideation and mood changes can occur, so subjects will be monitored closely at their weekly visits using psychometric measures of mood and suicidal ideation. The Columbia Suicide Severity Rating Scale will be used routinely to help identify subjects in need of further evaluation or intervention. Additionally, a DSMB will be employed to regularly monitor study safety (see section 5 below for more information). Subjects are allowed to continue to receive psychiatric treatment for any co-occurring disorders during the study.

8.D. BENEFITS TO SUBJECTS AND KNOWLEDGE TO BE GAINED:

Risk/Benefit Ratio:

Benefits to subjects include potential reduction in alcohol use induced by the medication. Free medical, laboratory, and psychiatric examinations are benefits provided to subjects. Most important, however, is the potential freedom from alcoholism and the serious impact that this may have on interpersonal, intra-psychic, occupational, familial, and economic aspects of the alcoholic's life if the treatments are successful. The benefit to society that would result from improved effectiveness in treating alcoholism is also significant, given the high societal cost of alcoholism. The identification of biomarkers (e.g., genetic variants) that predict better response to medication and limit side effects would benefit society greatly. The risk associated with MM is minimal. Although the pharmacological treatment carries some risks, ZNS is generally well tolerated. The potential risks of these treatments are minor compared to the risk incurred by individuals who, rather than receiving treatment, continue to drink heavily. Thus, the risk/benefit ratio appears most favorable toward the proposed treatments.

8E. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED:

As described in the main research document, veterans, and society in general, are in need of better treatments for alcohol dependence. More research is needed, and this trial proposes to study the effectiveness of a medication that has some evidence of efficacy, and is well suited for veterans. Alcohol dependence has a huge impact on society, and contributes to poor psychiatric outcomes as well. The findings of the proposed study could do a lot to advance treatment for veterans with alcohol dependence. The results will help to

optimize and personalize alcoholism treatment for veterans. The risk benefit ratio is discussed further in section 3 above.

8.F. DATA AND SAFETY MONITORING:

Data and Safety Monitoring Board (DSMB): Albert Arias, M.D., a board certified psychiatrist and the principal investigator of the proposed study, will be charged with the duty of determining the severity rating of adverse events. The study staff (P.I., co-investigators, clinical research coordinator) is responsible for collecting and recording all clinical data. As these results are collected, all toxicities and adverse events will be identified, graded for severity and assigned causality, reported to the required entities, and compiled for periodic review. After assigning causality, the P.I. will decide the course of action for the study participant. The P.I. will evaluate every adverse event and determine whether it affects the risk/benefit ratio of the study and whether modifications to the protocol or informed consent form are required. Serious adverse events will be reported to the West Haven VAMC/Bedford IRBs, as well as the DSMB, within 48 hours.

Reports of adverse events, protocol deviations, and any other relevant safety information (drop outs, etc.) will be reported to the DSMB every 6 months. DSMB members will review and decide whether the study should continue as planned, or if changes are needed, or if the study should be stopped. Teleconferencing will be performed to facilitate these discussions between the DSMB and research team as needed. The review process will be documented and reported to IRBs.

The DSMB is composed of persons not otherwise affiliated with the clinical trial who are experienced in various aspects of the conduct of clinical trials for the treatment of addictive disorders. We propose three investigators located here in Connecticut who are not directly involved in this trial – Declan Berry, M.D., Ph.D., Sherry McKee, Ph.D., and David Fiellin, M.D. as the membership of the DSMB. These three clinicians have appropriate expertise in substance abuse and psychopharmacology for this study. None of these three are directly involved with this proposed trial and consequently should not pose a conflict of interest. The members of the DSMB and all study Investigators will complete Conflict of Interest forms created by the HSS in accordance with NIH guidelines.

As noted above, precautions for pregnant or reproductive age women are in accordance with NIAAA requirements and this will be monitored as part of the DSMB. Women who are pregnant or breastfeeding will not be included in this study. Females must endorse adequate regular contraceptive use, and not plan on becoming pregnant during the timeframe of participation in the study. All adverse events in the taper/follow-up time-period will be reported to the West Haven VAMC/Bedford IRBs, with serious adverse events being reported within 48 hours. Any subjects thought to be at risk from drinking or psychiatric or medical disorders during the taper/follow-up period will be referred to services at West Haven VAMC, Bedford VA, or to other local health service providers.

All data and blood specimens will be stored without direct identifiable information, but will be identifiable via a linking code. We will collect saliva or blood for DNA. 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 in our VA alcohol clinical trials unit, or in the secured offices of the Laboratory of Psychiatric Genetics. 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 in the West Haven VAMC, 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 or later versions, a password-protected screen saver will be installed and configured to activate ten minutes after the computer has been idle. Information and data (including blood/saliva data) collected at the Bedford VA will be transmitted via VA guidelines.

Data used for safety monitoring will include serious adverse events, dropout rates and reasons for dropout, enrollment numbers, subject interviews, medication compliance, review of symptoms or performance status,

review of clinical/diagnostic test results, review of physical examination, review of vital signs, review of evaluation performed, protocol deviations, and blinded data. If it has been determined, for any reason, that there will be a suspension of this study, the PI will suspend enrollment of new subjects but continue intervention/monitoring of previously enrolled subjects if it is in the best interest of those subjects. We have determined that this study involves more than minimal risk to subjects, but that potential benefits outweigh potential risks of treatment.

TARGETED/PLANNED ENROLLMENT ON NEXT PAGE:

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Zonisamide for Heavy Drinkers

Total Planned Enrollment: 160

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	30	30
Not Hispanic or Latino	5	125	130
Ethnic Category: Total of All Subjects *	5	155	160
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	38	40
White	3	117	120
Racial Categories: Total of All Subjects *	5	155	160

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

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