Title: Zonisamide Treatment of Alcohol Use Disorder: an Evaluation of Efficacy and Mechanism of Action

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2. Project Title:
"Zonisamide treatment of Alcohol Use Disorder: an evaluation of efficacy and mechanism of action"

3. Purpose, hypothesis and key questions

Purpose: To comprehensively evaluate the efficacy of an anticonvulsant medication zonisamide (ZNS) for the treatment of alcohol dependence in civilians. We want to see if the medication works to reduce harmful drinking patterns, and try to determine whether medication response can be predicted by a few key factors such as genotype, the age of onset of alcoholism (early vs. late), or stress-reactivity. This protocol also contains translational sub-studies that will help elucidate the mechanism of action of the medication and determine subject characteristics that predict preferential response.

SPECIFIC AIMS: Zonisamide (ZNS) is an anticonvulsant medication for which evidence of efficacy in treating alcohol use disorders (AUDs) was obtained in two small placebo-controlled pilot studies. We propose to 1) add a civilian arm (N=160) to complement the existing VA/CSR&D study comparing ZNS to placebo over 16 weeks of treatment; 2) add important mechanistic and translational components to both trials (potential N=320) to elucidate the mechanism of action of ZNS and enhance our understanding of how anticonvulsant treatments reduce drinking. Importantly, there is no overlap between the VA/CSR&D funding, and the proposed NIH funding. So we will evaluate *efficacy, safety, and mechanism of action* of zonisamide in treating alcoholism.

Specific Aim 1) To evaluate fully the efficacy of and scope of effectiveness for ZNS in treating AUDs by adding a civilian arm (*N=160 randomized, 80 on ZNS and 80 on placebo*) to the CSR&D-funded study in veterans, using the same primary outcome (drinks per week) and secondary measures of drinking behavior as the veteran arm [i.e., heavy drinking days/week, percentage of subjects with no heavy drinking days (PSNHDD), craving, reductions in GGT]. Subjects will meet criteria for an AUD (DSM-5) and be heavy drinkers similar to the participants in the VA study. We hypothesize that ZNS will produce a significantly greater reduction in drinks per week than placebo (primary outcome alpha = .05). We also hypothesize that ZNS will significantly improve secondary measures of drinking (corrected for multiple comparisons). We will recruit civilians from the University of Connecticut Health Center (UCHC) and VCU's Institute for Drug and Alcohol Studies (IDAS)

Specific Aim 2) 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.

Exploratory Aim 1) To study genetic variation as a predictor of treatment response to ZNS using a convergent functional pharmacogenomics approach. This will be based largely on information gleaned from genomic analysis that has already been performed, although we will also perform a meta-analysis on data and samples on hand from previous clinical trials that are already completed. Those samples from previous studies will be genotyped using genome-wide assay, and merged with de-identified clinical trial data, consisting of items such as responses to assessments, demographics and other data collected during study visits (See section 6.E through 6.K for information on study visits) which may be pertinent to the overall study (all data and samples are de-identified) at Yale University. That data will be analyzed (in de-identified fashion) at both VCU and at Yale. VCU will host their own version of REDCap which may be used to store the data. Those findings will be used to generate methods of predicting outcomes and medication response in the ZNS trial data. All the ZNS trial subjects will be genotyped with

a genome-wide assay. We hypothesize that we can predict the response to medication based largely on a genetic risk prediction score (GRPS) generated from an empirically derived set of polymorphisms in genes known to be involved in the pathophysiology of AUDs and a stress-reactive endophenotype. We hypothesize that the ZNS treatment effect compared with placebo will be greater for subjects with higher GRPS in terms of reduced drinking. We will develop and refine this method in an available discovery samples from clinical trials of AUD via meta-analysis before testing it in the ZNS samples.

Exploratory Aim 2) 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. Alcohol Use Disorders Background.

Alcohol use disorders (AUDs) continue to be highly prevalent in the U.S. (lifetime prevalence estimated to be >30% in the U.S. general population, and >40% in military veterans) and have a large detrimental impact on society [[1-3], also unpublished data from the VA National Center for PTSD]. Because the FDA-approved medication treatments for alcoholism (naltrexone, acamprosate, disulfiram) have modest effects, there is a need for more efficacious pharmacologic treatments [4]. Anticonvulsants have shown evidence of efficacy in treating alcoholism. Zonisamide (ZNS) is an anticonvulsant and a promising potential treatment for AUDs. ZNS appears to have a number of advantages over existing pharmacologic treatments for alcohol dependence (AD), which include its easy once-a-day dosing and simple titration schedule, a favorable side effect profile, and efficacy in reducing weight/overeating. ZNS reduces anxiety and craving in patients with AUD.

4.A.1. Further study of ZNS advances the development of pharmacologic treatments for AUDs: Despite a recommendation from the NIAAA to offer medication as a first line treatment for AUDs, their use has not been widely adopted by physicians. Many people with an AUD that might benefit from a pharmacologic treatment never receive it [5, 6]. A study of barriers to the use of medications found that side effects were thought to present a significant barrier to use, based not only on patients' reports, but the reports of physicians [6]. ZNS appears to be better tolerated than some other available treatments for reducing drinking such as disulfiram or topiramate. ZNS's beneficial effects on weight and overeating behavior offer an additional incentive to many patients to use the medication, and may facilitate adherence compared to that with naltrexone (NTX) or gabapentin [7, 8]. The study by Mark et al. [6] showed that a perceived lack of research into medication efficacy was a barrier to medication use in practice. Thus, there is a great need for research evaluating the efficacy of new medications. *The research proposed here will help to address that need by testing ZNS's efficacy in a well-powered study of regularly heavy drinking subjects with DSM-5 AUD.*

4.A.2. ZNS to treat AUD/The Pharmacology of ZNS:

4.A.2.a. Treating AUDs with Anticonvulsants:

The potential utility of anticonvulsants to reduce the risk or severity of relapse was demonstrated initially in studies by Mueller et al. [9] and by Brady et al. [10] showing some benefits compared to PLC treatment. Johnson et al. [11] 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, topiramate was again found superior to PLC with a moderate effect size [12]. A more conservative analysis of the topiramate data, which assumed a return to baseline drinking levels for dropouts, reduced the effect on heavy drinking by about half. Critics have brought attention to the frequency and severity of side effects from topiramate, which limit its effectiveness [12-14]. A recent study showed a moderate dose of topiramate to be fairly well tolerated and efficacious [15]. A placebo-controlled trial of

gabapentin in patients with AD showed significant benefit with the medication, although the dropout rate was high [16].

4.A.2.b. The Rationale For ZNS Treatment Of AUDs:

ZNS is FDA approved for the adjunctive treatment of partial seizures in adults with epilepsy, and widely available as a cheap generic medication. Strong support is available from animal models for the use of ZNS to treat AUDs. Rats chronically administered topiramate or ZNS showed reduced consumption of an ethanol-sucrose solution [17]. Four 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** showing significantly greater improvement with ZNS **[18].** Two other clinical trials were open-label [19, 20] 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 craving and in the amount of alcohol consumed with ZNS compared to PLC [21]. A trial comparing ZNS to diazepam in treating the alcohol withdrawal syndrome found **ZNS more effective, and ZNS treated subjects had less craving, less anxiety**, and less sedation [22]. In these studies, ZNS was well tolerated, and few participants dropped out.

Most recently, a small (n=19 subjects on ZNS) placebo-controlled study of ZNS for AUDs was completed at Boston University as part of a larger trial comparing levitiracetam, topiramate, ZNS, and PLC [23]. In this 16-week study, ZNS 400mg daily was found to significantly reduce percent drinking and percent heavy drinking days more than PLC, with effect sizes similar to topiramate. In general, side effects were less with ZNS than topiramate. ZNS was well tolerated in that study with some caveats. ZNS did have some cognitive side effects, though not across as many domains as topiramate, and to a lesser extent. One subject on topiramate developed metabolic acidosis, and none in the ZNS group did. 17% of topiramate subjects reported paresthesias, though none of the ZNS subjects did. One serious adverse reaction (suicide attempt) was reported in the ZNS group, though it was rated as “only remotely related to ZNS”. Anticonvulsants as a class are thought to carry an increased risk of suicidal ideation and behavior. The observed benefits of ZNS as a treatment for AUD suggest it should be studied further.

4.A.2.c. 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 [24]. ZNS blocks T-type calcium channels [24]. ZNS indirectly facilitates GABA and indirectly reduces glutamate neurotransmission, unlike the direct effects exerted by topiramate on GABA-A, AMPA, and kainate receptors [25, 26]. ZNS effects on GABAergic neurotransmission are highly complex, but ZNS facilitates GABAergic inhibitory neurotransmission overall while reducing glutamate release from neurons [26]. ZNS also acts on Excitatory Amino Acid Transporters (EAATs), which are membrane bound glutamate transporters thought to play a role in the pathophysiology of AUDs [27]. In the hippocampal and frontal brain areas of rats, ZNS up-regulated and enhanced the function of the glutamate transporter EAAT3/EAAC1 and down-regulated the GABA reuptake transporter GAT-1 [25]. By this mechanism, ZNS increases glutamate clearance and potentiates GABAergic transmission by increasing tissue and synaptic GABA levels. ZNS’s effects on GABA may explain its anxiolytic properties in patients with AUD and patients with refractory anxiety [22, 28, 29].

ZNS causes reversible MAO-B inhibition, an effect that **is not** associated with the side effects attributed to irreversible MAO inhibitors, so hypertensive crises or dietary restrictions are not concerns [30, 31]. ZNS has direct effects on serotonergic and on dopaminergic neurotransmission [32, 33]. ZNS increases serotonergic and dopaminergic output over time, an effect that is biphasic in terms of dose relationship; thus at a certain point, output of these neurotransmitters plateau, although output remains elevated relative to baseline.

4.A.2.d. ZNS Pharmacokinetics: Hepatic metabolism of the drug occurs with acetylation of ZNS to N-acetyl ZNS and CYP3A4 mediated reduction to 2-sulfamoylacetyl phenol. The plasma elimination half-life is about 63 hours [34, 35]. 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 dosage adjustment but such subjects will not be included in this study (see exclusion criteria).

4.A.2.e. ZNS Dosing Rationale for AUD treatment: ZNS is typically used efficaciously in the range of 400-600 mg/day in adults with seizure disorders [36]. Similarly, clinical trials for weight reduction in obesity, and for treatment of binge eating disorder have employed ZNS target doses in the range of 400-600 mg/day [7, 8, 37, 38]. 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. Topiramate appears to be efficacious in reducing weight, binge eating, and drinking in the range of 200-300 mg/day, though significant weight loss can occur at lower doses [11, 12, 39-42]. In our pilot study, a target dose of 500 mg/day was selected based on ZNS's general clinical behavioral similarity to topiramate at an approximate analogous 2:1 dosing equivalency between the two drugs with regard to appetitive behaviors. The mean maximal dose of ZNS in the pilot study was 430 mg/day. The data from our ZNS pilot study suggest that a slightly higher dose of 600mg daily may optimize effects on reducing drinking, and should be well tolerated. Titration rates of 50-100 mg every 1-2 weeks have been used safely [43, 44].

4.A.3. Using a micro-longitudinal approach to examine a medication's mechanism of action and pharmacogenetic interactions:

Using this method, they demonstrated an interesting and complex pharmacogenetic interaction with topiramate and a *GRIK1* single nucleotide polymorphism (SNP, rs2832407) [45]. *GRIK1* is the gene that encodes the GluK1 kainate receptor subunit, and rs2832407 (C/T) is an intronic SNP that has been associated to the risk of developing AUD, with the C allele being the risk allele. They performed a mediation analysis using the daily micro-longitudinal data investigating the role of "self-efficacy" in changes of drinking behavior. They found that topiramate's effects on drinking level were moderated by rs2832407, such that C-allele homozygotes treated with the active medication showed the greatest increases in self-efficacy across the 12-week trial. Further, the effect on self-efficacy (measured in the early evening) fully mediated the reduction by topiramate of nighttime drinking level. This is important because the mediation analysis points to causal factors.

4.A.4. Pharmacogenomics 2.0: Pharmacogenetic studies of alcoholism treatment have yielded promising findings, yet translating this information into clinical practice remains difficult because of many conflicting results. Thus, the current state of applied pharmacogenetics for treating AUDs is very limited, and is lagging behind other fields. We are developing a new method for pharmacogenomic optimization of medication response in alcoholism treatment. This method seeks to identify and prioritize the most succinct list of clinically relevant genetic loci for predicting a given phenotype. This "Convergent Functional Pharmacogenomics" approach converts data from that succinct set of highly relevant variants into an averaged or total score referred to as the **"genetic risk prediction score" (GRPS)**, which can be used in statistical analyses as a continuous single variable, thus eliminating the need to perform multiple comparisons. In order to do that appropriately, the approach needs to be informed by previous behavioral genetic and pharmacogenetic research, developed in discovery samples, and validated in replication studies. Much of this work for predicting risk of developing alcohol dependence has been done, and Drs. Gelernter (co-investigator) and Kranzler (consultant) made significant contributions to this work [46]. A similar but more limited approach has been applied in smoking cessation treatment research, though not yet in alcoholism treatment trials.

5. Significance:

AUDs are highly prevalent in civilians and in veterans, and the prevalence may be increasing over time, at least for civilians. ZNS is an extremely promising medicine for treating AUDs and managing other clinical problems including psychiatric disorders. ZNS is an affordable, generic anticonvulsant with unique actions on the major neurotransmitter systems

involved in alcoholism, and it has neuroprotective effects. We completed a randomized, placebo-controlled pilot study of ZNS in treating AD that showed significant reductions in heavy drinking, overall drinking, and alcohol craving. ZNS was very well tolerated in this study. In this application, we propose a larger (N = 160), 16-week, randomized, double-blind, placebo-controlled, efficacy study of ZNS in reducing drinking and improving outcomes in a representative population of heavy-drinking civilians with AUD.

6. RESEARCH PLAN/EXPERIMENTAL METHODS:

6.A. CLINICAL TRIAL METHODS OVERVIEW: Overall trial design: ZNS treatment of civilians with AUD: The proposed study, which is registered on clinicaltrials.gov (NCT02900352), will be a two-arm, parallel-groups comparison of ZNS and PLC on outcomes of reducing and eliminating heavy drinking in subjects with AUD. We will conduct a 16 week, randomized, double-blind, placebo-controlled study in N=160 regularly heavy drinking subjects with DSM-5 AUD. We will enroll patients whose goal is to reduce their drinking to safe levels or to stop drinking. At each visit, all patients will receive Medical Management [47], which was developed for the COMBINE Trial and which we modified to be relevant for both reducing heavy drinking and promoting abstinence. Random assignment to treatment group and double-blind conditions will be maintained throughout the study. Raters will be trained in the reliable use of all assessments. We will use serum GGTP, Phosphatidyl Ethanol (PEth), Ethyl Glucuronide, and Ethyl Sulfate (EtS) to validate patient reports. Following a 1-2 week pre-treatment assessment period, patients will receive 16 weeks of treatment. 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 Sinha [48] will be performed with subjects after screening but before starting medication (baseline stress/impulsivity), and then a second lab will be performed between weeks 9-16.

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, which will be assessed at visits as described in Section 6.F.2 "Counseling"). 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.**

6.B. Subjects *and recruitment*: The clinical trial portion of this study is being conducted at two sites; (1) VCU's Institute for Drug and Alcohol Studies (IDAS) and (2) the University of Connecticut Health Center (UCHC) in Farmington CT, which also has its own NIAAA-funded Alcohol Research Center. This Project will benefit from the expertise and resources for conducting clinical trials at both centers. Both sites recruit from different catchment areas and have good records of subject recruitment. N= *160* subjects will be randomly assigned to receive

either ZNS (80 subjects) or PLC (80 subjects). Note that the translational sub-studies (genetics, and stress reactivity lab) will be performed on both the civilians and veterans, so they will occur at all 4 total sites for both the civilian and veterans studies: VA Connecticut (the West Haven VAMC), UCONN Health Center, VCU IDAS, and the RichmondVAMC. We anticipate an upper limit of enrollment to be N=200, however for the study we have a participant target goal of N=160.*For the sake of simplicity, we describe those procedures here written for the civilians only, but they will be added separately to the veterans study protocol also. The funding for the translational sub-studies will come from NIAAA.* We would like to reserve the right to enroll veterans here at VCU IDAS for the translational components of the study only, if that is easier logistically than running the translational components at the Richmond VAMC. The Richmond VAMC will recruit veterans for the study, using their specialized protocol and these participants will be given the option of coming to VCU for the add-on stress lab and IVR components.

6.C. Clinical Trial Inclusion and Exclusion Criteria:

Participants: *N=160* men and women **civilians** from the greater Richmond area are being recruited through radio, bus, and print advertising, online advertising, study web sites, referrals, and flyers at VCU facilities and community areas (i.e., coffee shops, grocery stores, etc.), as well as surrounding area clinics. We will also utilize HM20000294 in which participants indicated if they would like to be contacted for future studies in order to identify and contact potential participants

Inclusion Criteria (each subject must meet all of the following to participate): a) age 21-70 years, inclusive; b) regular heavy drinkers as defined by averaging ≥ 2 heavy drinking days per week over the 90 days baseline pre-treatment timeline follow-back (TLFB), and ***current DSM-5 AUD*** that recognize a need to reduce or stop drinking; c) willingness to provide written, informed consent to participate in the study; and d) for 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. Section 6.I reviews medications allowed and not allowed during study.

Exclusion criteria are: a) a current, clinically significant physical disease [i.e., neurologic, renal, rheumatologic, gastrointestinal, hematologic, pulmonary, endocrine, cardiovascular, hepatic, or autoimmune disease] on the basis of medical history, physical examination, or routine laboratory evaluation that, in the context of the study would represent a risk to the subject, or significant laboratory abnormalities related to hepatic function such as marked elevations of hepatic aminotransferase levels (i.e., AST and ALT) or direct bilirubin. Other specific exclusionary disorders include; b) history of clinically significant renal calculi or renal failure; renal compromise (defined by an elevation of serum creatinine above our laboratory's limit of normal);c) history of hypersensitivity to ZNS, or any sulfonamide, Stevens-Johnson Syndrome, or history of any severe drug allergic reaction; d) current clinically significant blood dyscrasia, e) history of seizure disorder; f) use of any of a number of medications that might prominently influence drinking patterns or cause risk of harm or injury (e.g., FDA approved medications to treat AUD, chronic use of opioid pain medication or benzodiazepines, tramadol); g) schizophrenia, bipolar disorder, or substantial suicide or violence risk on the basis of history or psychiatric examination; h) currently dependent on opioids or benzodiazepines; i) are considered to be unsuitable candidates for receipt of an investigational drug; j) 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.

6.D.Temporal Sequence of Study Procedures: Following telephone screening to determine initial eligibility, patients will be invited to the clinical site for an in-person visit. At the first in-person visit, informed consent will be obtained and patients will undergo a screening interview

to assess inclusion and exclusion criteria. Patients excluded at any point in the recruitment process will be referred for appropriate treatment based upon consultation with the study physician (See Section 6.I "Other Treatments Allowed During the Study" for a more detailed explanation). If subjects are unable to complete the entire screening procedures in 1 visit due to their schedule, they may be allowed to return for additional visits if needed prior to baseline.

6.E. Schedule of Visits:

6.E.1. Visit 1 (Screening Visit): At the screening visit (visit 1), patients will be asked to provide informed consent. The PI and/or the study Nurse Practioner (NP) will obtain a medical and psychiatric history, and perform a physical exam. Substance use data for the 90 days prior to the screening visit will be collected via the Timeline Follow-Back (TLFB) Method. Blood or saliva and urine samples will be taken for routine clinical laboratory evaluations (including GGTP, ETG/ETS, and PEth), drug screening, pregnancy testing (in females of reproductive potential), and DNA extraction. All projected amounts will be discussed in the consent form, we estimate the total amount of blood drawn to be approximately 10 TBSP for the entire study, but additional labs may need to be repeated at the discretion of the PI to ensure participant health and safety. Additional blood will only be drawn if determined medically necessary. Screening will last about 3-4 hours total.

6.E.2. Visit 2a (Baseline Visit): After the screening visit, eligible patients will undergo the baseline visit prior to randomization. They will complete a packet of questionnaires and the research assistant will train them to record data on alcohol consumption, medication administration and other daily variables using IVR, which is a self-reported assessment of mood, drinking habits and attitudes towards alcohol. Baseline impulsivity will also be measured before imagery using the Barrett Impulsivity Scale [51]. The subject begins a 7-week titration phase, during which the ZNS (or matching PLC) dosage will be titrated up as indicated below in Table 1, to a maximum of 600mg/day. Subjects will receive compensation for all visits, including follow-up visits (see Table 4). Compensation will not be prorated. Participants will be offered transportation assistance if needed to return home from study visits in the form of bus tickets or taxi rides, as long as these trips are within a 20 mile radius or are on the bus lines. Study staff will work with the participant at individual study visits to determine which mode of transportation is most feasible for the participant.

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.E.3. Visit 2b (Baseline Stress response lab): *THIS LAB SESSION IS DESCRIBED IN FULL DETAIL BELOW IN SECTION 6.J*. Subjects will be scheduled for this ~ 4-6-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 six 5 minute long scripts that will be read and audiotaped; two describe a very stressful event in the person's life, two describe a neutral event, and two describe a pleasant alcohol-related event. Then subjects sit in an isolation booth and listen to the audiotapes sequentially while psychological measures of craving and anxiety are recorded. Impulsivity/risk-taking [via the Balloon Analogue Risk Task (BART)] will be recorded at the start of each lab session [50]. Subjects are taught to relax for 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 9-16 of being on the medication. All subjects enrolled at the VCU IDAS site will have their lab sessions at the IDAS facility 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. We anticipate that we will still be able to evaluate primary and secondary outcomes and having stress lab data for less than N=160 will not impact our overall results in a significant manner.l*

6.E.4. Visits 2c-11 (Treatment and End-of-Treatment Visits): Patients will first receive counseling and study medication during a treatment session (visit 2c) scheduled on the same day as the baseline assessment. Patients will be given study medication consisting of ZNS or matching PLC and titrated up to a maximum of 600 mg/day of ZNS (see Table 1). We will use blocked stratified randomization with treatment site (Yale versus UCHC) and use of antidepressants/psychotropic (yes/no) as the stratification variables, and block sizes of 4 in each stratum to achieve treatment balance throughout the randomization process. During the 16-week treatment period, patients will come in for a visit within 1 week after starting the study medication (week 1). They will then come in on weeks 3, 5, 7, 9, 11,13, and 16. After completing a two-week taper, patients will return on week 18. (Note: a research staff member will call the patient on weeks 2, 4, 6, 8, 10, 12, 14, 15, and 17. The purpose of this call will be to check in with the patient and make sure they do not have any questions and that they are tolerating the medication.) At each visit, the patient's breath alcohol level (BAL), weight, and vital signs will be measured. Participants will be expected to have a BAL under the legal limit (.08) in order to participate in visits. At screening, all female subjects will have a blood pregnancy hCG quantitative titer drawn to detect pregnancy. Urine samples will be collected at each visit for drug screening and once monthly for female subject's pregnancy testing. Samples for ETG (urine) and PEth (blood) will be collected as indicated in Table 2. Patients will then complete questionnaires and be interviewed by the study nurse about their concomitant medications, adverse events, and protocol compliance. At every treatment visit (i.e., for a total of 9 sessions), the nurse will deliver the MM intervention. At midpoint, Week 9, Baseline impulsivity will also be measured before imagery using the Barrett Impulsivity Scale [51]. At the end of treatment, the research assessment will be repeated, including a query of the patient's belief as to their treatment condition (using the Medication Questionnaire; MED-Q). Blood samples for measurement of serum GGTP will be obtained to assess the validity of self-reported drinking. All patients will be asked to complete an end-of-treatment evaluation and to complete all scheduled assessments to facilitate intent-to-treat (ITT) analyses. Participants who discontinue the medication before the typical Endpoint will be given the option to participate in an abbreviated version of the visits starting at what would normally be the visit labeled Week 16 onward. This will also allow us to monitor them for safety while tapering (if needed).

6.E.5. Visit 10b (Stress Lab Session 2): This visit will occur between weeks 9-16 of being on the study medication. The session will use the same audiotapes created for the baseline stress

lab. The session will be identical to the baseline stress lab (assessments), with the exception of the randomized order of the presentation of the audiotapes.

6.E.6. Visit 12 (Follow-up): A follow-up visit will occur approximately 3 months after the patient completes the 16 weeks of the study medication. This visit will last approximately 1-2 hours and the patient will be asked to complete the same surveys they had completed during the weekly/biweekly visits.

6.F. Study Treatments: Throughout the study, we will maintain double-blind conditions regarding medication condition. We will break the blind in the event of a severe adverse event wherein knowledge of the identity of the study drug received by the participant is necessary for effective emergency treatment of the event. MM will be delivered by a study nurse who is experienced in its use in alcohol pharmacotherapy trials. The PI will meet with the patient at the beginning of treatment and discuss clinical management with the nurse weekly. The PI will evaluate the patient for severe or persistent adverse effects. At each visit, the nurse will dispense study medications prescribed by the physician.

6.F.1. Medication Condition: The maximal dosage of ZNS to be used in the present study is 600 mg/day. We will use a seven-week titration period. The dosage of medication will be increased only as tolerated and patients experiencing intolerable adverse effects will have their dosage decreased gradually to the highest tolerated dosage. The study nurse (in consultation with the PI) and the PI will provide guidance for patients as they increase their medication dosage, per the titration schedule. ZNS will be purchased commercially and formulated by the VCU and UCHC research pharmacies respectively; PLC capsules will be formulated to match the active medication, so that inspection of the capsules cannot allow them to be differentiated.

6.F.2. Counseling: At each treatment visit, all patients will receive MM, a medically oriented intervention that supports the use of pharmacotherapy and maximizes medication adherence in AUD treatment [47]. Clinicians with minimal specialty training but who are knowledgeable about AUD can deliver this brief and effective intervention, which has been widely used. In MM, the clinician highlights the patient's AUD symptoms and need for treatment. The patient is advised to reduce or stop drinking, is educated about AUD, is provided a rationale to take medication for its treatment, and is instructed on the importance of daily medication adherence. The clinician and patient jointly develop an individualized medication adherence plan; and the patient is given information on the medications. MM enhances adherence, providing treatment comparable to what is feasible in most medical settings. It is unlikely to obscure a medication effect on drinking outcomes.

The first MM session will last 30 minutes and subsequent sessions 20 minutes. During all sessions, the study nurse will check the patient's BAL, vital signs and weight, adverse effects, medication adherence, and concurrent medications; perform a brief assessment of the patient's drinking and general functioning; and make recommendations for the patient to follow until the next visit. Patients with severe psychological symptoms (e.g., suicidal thoughts) will be withdrawn from treatment and referred for appropriate clinical care.

6.F.2.a. Ensuring Adherence to MM Content and Procedures: Our study nurse will undergo training from the study nurse at UCHC which will entail a review of the protocol and MM manual, role-play, practice of initial and follow-up sessions, and review of taped practice sessions until adequate performance is achieved. Our study nurse will also monitor the MM for this study (i.e., by listening to 10% of recorded visits, evaluating adherence to MM principles, recording the total time in the treatment session, assessing the therapeutic relationship, reviewing the achievement of reduced drinking goals and clinical improvement during treatment, and providing individual feedback). One session from each subject will be reviewed with equal frequency for each of the 10 different MM sessions. Monthly protocol adherence meetings will be held with the nurse to assure protocol adherence.

6.G. Assessments: We include measures from different sources (see **Table 2**) to cover the various domains in which alcohol treatment may exert an effect and to corroborate self-reported treatment effects.

Study data will be collected and managed using REDCap electronic data capture tools hosted at VCU. 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 [52].

6.G.1. Laboratory/Medical Assessments: These assessments serve to: 1) screen patients for medical exclusion criteria, 2) assess potential adverse effects of ZNS, and 3) corroborate self-reported drinking. Prior to entrance into the study, each patient will receive a physical exam, urinalysis and urine toxicology, CBC, a chemistry panel [which includes electrolytes, liver enzymes (ASAT, ALAT, GGTP), bilirubin, uric acid, BUN, and creatinine], and pregnancy testing. Bicarbonate levels will be every 4 weeks because ZNS can cause metabolic acidosis; pregnancy testing and a CBC will also be repeated at the midpoint, which is planned to be week 9 but may be adjusted per patient visit needs. If a patient reports being pregnant or tests positive, she will immediately be excluded or withdrawn from treatment with medication, referred for obstetric evaluation, and advised to discontinue all drinking. At the midpoint (week 9) and endpoint (week 16), GGTP will be repeated to corroborate self-reported alcohol consumption. The patient will be in the downward titration phase of the medication at this point (See Table 1: Medication Titration Schedule). We will also obtain Ethyl Glucuronide (EtG), Ethyl Sulfate (EtS), and Phosphatidyl Ethanol (PEth) as biomarkers to verify subjective claims of drinking during the study.

6.G.2. Psychological/Behavioral Assessments: ZNS is hypothesized to have its greatest influence on alcohol consumption. The assessments listed below measure multiple outcome criteria, because a reduction in drinking may not result in improvement in other domains.

Table 2: Schedule of Assessments

			Study Week									
	SC	**BL**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**16**	**18**	**28**
Surveys/Procedures												
Overview and Consent	x											
Demographics	x											
Locator Information	x											
SCID-V	x											
Medical History/ Physical/Psych Exam	x											
FHAM	x											
Table 2 Continued			**Study Week**									
	SC	**BL**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**16**	**18**	**28**
Neurocognitive panel (Trail making test A & B; Verbal Fluency (FAS); RAVLT; Brown Visual Learning Test (BLT)		x					x			x		x
AUQ		x	x	x	x	x	x	x	x	x	x	x
Barrent Impulsivity Scale		x					x					
CIWA	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
PCL-5		x	x	x	x	x	x	x	x	x	x	x
PHQ-9		x	x	x	x	x	x	x	x	x	x	x
SAFTEE		x	x	x	x	x	x	x	x	x	x	x
STAI		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
MM		x	x	x	x	x	x	x	x	x		
IVR Daily Reports			x	x	x	x	x	x	x	x		
AADUD	x									x		x
AEQ		x					x			x		x
CAPS-5		x					x			x		x
CGI-I					x		x		x	x	x	
CGI-S		x										x
DMQ		x					x			x		x
LSCR	x											
PSS		x			x		x		x	x		x
Q-LES-Q		x								x	x	x
RAND SF-12		x								x		x
SCID Section E										x		x
SCID-II (antisocial)		x										
SIP		x								x		x
SLEI		x			x		x			x		x
SORT	x											
SRE		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/blood pregnancy test	x	x	x	x	x	x	x	x	x	x	x	x
Breathalyzer/Vitals/Weight	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

Table 2 Notes:

(1) Week 9 is the study midpoint; (2) TLFB data will be collected at each visit to cover the period since the last visit (baseline will be 90 days prior to randomization); (3) IVR calls will be made daily and will measure drinking behavior, craving, anxiety, and medication usage over the preceding 24-hour period. (4) **Abbreviations:** SC: screening; BL: baseline; TIPI: Ten-Item Personality Inventory; all other abbreviations can be found under the assessments sections of the project description. (5) Urine pregnancy testing will be performed at each visit for females of childbearing potential and a serum pregnancy test will be performed monthly, as needed, to rule out early pregnancy.

6.G.3. Areas assessed only at intake:

***a. Sociodemographic/general patient information*:** During screening, an assessment of medical history, personal and family history of alcoholism, marital status, educational and

occupational information and substance abuse treatment history will be obtained, along with the individual's self-identified ancestry.

***b. Locator information*:** At the time of enrollment in the study, the research coordinator will select patient locators on the basis of relationship to the patient, duration and current status of relationship, frequency of contact with the patient, and willingness to participate. Locators are contacted when efforts to reach a patient are unsuccessful, which enhances retention of patients in treatment and data collection.

***c. Psychiatric diagnosis*:** The Structured Clinical Interview for DSM-5 (SCID) will be used to classify patients according to the presence or absence of standard psychiatric disorders according to DSM-5 criteria. The clinical trials version is now available [53]. We may opt to use an online version for ease and clarity.

***d. Family history of alcohol dependence*:** The Family History Assessment Module [54] systematically queries the patient about the presence of an alcohol use disorder (AUD) in relatives. The patient will provide information concerning parents' and siblings' history of alcohol use without their being identified.

e. History of stressful events and trauma: The Life Stressor Checklist (Revised), a 30-item lifetime inventory of very stressful or traumatic events.

6.G.4. Areas assessed only at treatment endpoint:

a. Overall condition at the end of treatment (for early withdrawal from the study): The Early Termination Form, indicating the patient's level of functioning at termination, will be completed by the study nurse for any patients that leave treatment prematurely. The form is used to identify the reasons for early termination (e.g., symptomatic failure, adverse effects) and other relevant circumstances.

***b. Integrity of the double blind*:** The Medication Questionnaire (MED-Q) was developed to evaluate the masking procedure and will be completed by the patient at the midpoint (week 9) and end of treatment. Patients who are unable to return for the endpoint and are willing to complete the assessments will be mailed questionnaires (with a stamped envelope to facilitate their timely return) and then be interviewed by telephone to collect all information. Such subjects will be paid the same amount as if they actually attended the endpoint visit to complete those endpoint assessments.

6.G.5. Areas assessed at intake, end of treatment, monthly, or at each visit:

a. Alcohol use patterns: The Timeline Follow-back (TLFB) [55] will be used to estimate past 90-day drinking at intake and at every treatment visit going back in time from the last assessment. This interview procedure will provide quantity/frequency of alcohol consumption data for each day during the period prior to the interview. The TLFB is reliable and valid when used by trained interviewers. However, it is less useful than daily measures for detecting patterns of alcohol consumption that vary on a day-to-day basis [56, 57]. 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 the PI.

b. Alcohol craving; will be assessed at each treatment visit with the Alcohol Urge Questionnaire (AUQ), [58].

c. Alcohol-related problems: The Short Index of Problems (SIP). The SIP, a 15-item instrument that is a subset of the 50-item DrInC [59], measures alcohol dependence symptoms

and medical, psychological, social, occupational, and legal problems. To reduce respondent burden, we chose to use the SIP which, like the DrInC, measures a single factor of alcohol-related problems (61). The Quality of life enjoyment and satisfaction survey (Q-LES-Q)[60] (REF) will be used to assess quality of life in subjects.

d. Drinking motives and expected alcohol effects: 1) Drinking Motives: Drinking motives will be measured with the Drinking Motives Questionnaire [DMQ;[61, 62] to explore potential changes as a result of treatment in drinking motives. This instrument contains 20 items with 4 subscales, drink to a) cope motives (e.g., "Because it helps when you are feeling nervous or depressed"), b) conformity motives (e.g., "Because it helps me fit in"), c) enhancement motives (e.g., "Because it's fun"), and d) social motives (e.g., "Because it makes a social occasion more enjoyable"). The DMQ will be administered at baseline and for those subjects who continue to drink again at midpoint, end of treatment and at the 3-month follow-up visit. 2) Alcohol expectancies will be assessed with 24 items from the Alcohol Effects Questionnaire [AEQ;[63] probing 4 positive expectancy subscales (social and physical pleasure, aggression and power, social expressiveness, and relaxation and tension reduction) and 1 negative subscales (cognitive/physical impairment) to explore potential changes as a result of treatment with zonisamide. The AEQ will be administered at baseline and for those subjects who continue to drink again at midpoint, end of treatment and 3-month follow-up visit. 3) Self Rating of Effects of Alcohol (SRE) [64] is a widely used measure of number of drinks subjects report are needed to produce typical alcohol effects (alcohol sensitivity) during the first use of alcohol period in one's life, the past 3 months or period of heaviest use. The SRE will be administered at baseline and for those subjects who continue to drink again at end of treatment and 3-month follow-up visit.

e. Psychological symptoms: 1) The Physician's Health Questionnaire (PHQ-9), a validated 9-item self-report measure of depressive symptoms with a total score of 0-27 [65, 66] will be administered at each visit. 2) The State-Trait Anxiety Inventory will be used to measure anxiety symptoms at each visit [67]. 3) The Columbia Suicide Severity Rating Scale, C-SSRS [68] evaluates suicidal risk. A study nurse or research team member will administer the C-SSRS at each study visit and, if rated 4 or 5 (i.e., clinically significant suicidal ideation), the PI will be consulted to decide on the appropriate clinical management. 4) The RAND 12-Item Health Survey (SF-12)[66] (64), a self-report measure of life functioning in various domains, will be completed at study baseline, endpoint (week 18) and follow-up. We will focus on the mental health component of the SF-12. 4) Monthly Stressful Life Event Inventory: This is a 34-item questionnaire asking subjects to report and any stressful events in the interim period (SLEI). 6) Perceived Stress Scale, a ten item scale measuring perceived stress [69]. PTSD symptoms will be measured by the Clinician-Administered PTSD Scale for DSM-V (CAPS-5) and the PTSD Checklist for DSM-V (PCL-5)[70, 71]. CAPS-5 will be conducted at baseline, week 9, week 16, and follow-up; PCL-5 will be conducted at baseline, each treatment visit and follow-up.

f. Neurocognitive measures: To evaluate the potential cognitive side effects of zonisamide in subjects with alcohol use disorder, we will use a panel of brief neuropsychological tests covering multiple cognitive domains at baseline, midpoint, endpoint and 3 month follow up visit. 1) Psychomotor / visual motor tracking Trail Making Test A, subjects are instructed to draw a line connecting sequentially 25 numbers distributed on a sheet of paper, time in seconds required to complete the task recorded. 2) Executive Function Trail Making Test B. In this test subjects are instructed to draw a continuous line connecting numbers and letters distributed on a sheet of paper in alternating fashion (e.g., 1, A, 2, B, 3, C, etc.). The score is the time in seconds required to complete the task. 3) Verbal Fluency Phonetic fluency – FAS letter fluency/word naming, participants are instructed to verbally generate words that begin with the letters F, A, and S in three separate, 1-min trials. Proper nouns and multiple words using the same stem with different suffix (e.g., friend, friends, friendly) were scored as incorrect. Total words for the three trials are summed. Semantic category fluency – animal naming. For the category fluency task, participants are instructed to say "the names of as many animals that they could think of" in a 1-minute period. 4) Verbal learning and memory: Rey auditory verbal learning test (RAVLT) measures short-term verbal memory and rate of learning. In this test subjects are read a list of 15 unrelated words repeated over 5 trials and asked to repeat the list after each trial. Words may be recalled in any order. The number of words recalled during each

trial is summed. 5) Visual learning and memory: The Brown Location Test (BLT) is a visual learning task independent of verbal, global intellectual, fine motor or drawing skills that consists of five recall learning trials, an interference trial, and a short delay recall. In this task, presented on a computer screen, subjects are shown a series of 12 images for 4 seconds each that contain one red dot in different locations on a common field of 56 non-symmetrically placed circles. Subjects are then presented a page with the 56 non-symmetrically placed circles and instructed to place 12 red dots at the positions in which they appeared in the prior presentations. Following five red dot learning trials an interference trial is presented using one trial of 12 images with black dots in different locations on the circle array and asked to indicate the locations of the black dots. A final blank 56 circle array is provided and subjects asked to indicate the positions of the red dots learned in trials 1-5. Total correct for trials 1-5 sum, interference and delayed recall are scored. Normative data are available for each of these neuropsychological tasks[72-76].

g. Medication adverse effects: *Patients* will provide subjective reports of side effects at each study visit using the Systematic Assessment for Treatment Emergent Effects (SAFTEE) interview [77], a widely used measure of adverse events. A standardized approach was developed for use in alcohol treatment trials [78].

h. Measures of treatment received: Records of medication taken will be kept and patients will be asked to return the unused portion of study medication at each visit. The nurse will also record the number of contact hours patients have been exposed to any alcohol treatment outside of the study.

6.G.6. Areas assessed daily: 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. [45, 79, 80]. 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% [81]]. Patients are paid $2 for each telephone call completed and an additional $6 for each week in which they complete 6 or more of the 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 [79] and 83.5% in a study of topiramate [15].

a. Daily subjective measures assessed with IVR: These include 4 items assessing anticipated positive outcomes for drinking later that day. The items, adapted from existing expectancy scales (67-69), correspond to the commonly identified expectancy domains of general pleasure, tension reduction, social expressiveness, and enhanced sexuality. Responses will be made on a 4-point scale (0=not at all to 4=extremely likely). Similarly, subjects will report on their craving, self-efficacy for controlling drinking, and anxiety levels.

b. 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 (44, 65). The time of the calls (5-8 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 UCHC, but will be implemented at all three sites. Cellphones or

prepaid phone cards will be provided to subjects without a reliable phone during the study. Staff will determine participant's needs and work with them to determine a feasible option.

c*. 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) [82].

6.H. Exploratory Pharmacogenomic Analysis: DNA samples will be prepared on site at each site**.** Genotyping will be carried out either in the VCU Psychiatry genetics laboratories, or the Yale affiliated Laboratory of Psychiatric Genetics with the Illumina genomewide microarrays and GenomeStudio software, using standard quality control measures. Using PLINK software, we will obtain genotypes for 66 SNPs in the 11 genes identified by Levey et al. [46] using a CFG method as being predictive of AUD risk, and which are also thought to be associated to an endophenotype of stress-driven drinking. We will genotype data from ancestry informative markers (AIMs) contained in the HumanCore24 array to derive ancestry proportions to be used in the analyses to adjust for population genetic structure [83]. This 11 gene panel of key alcoholism related genes includes that encoding the alpha-synuclein protein (*SNCA*), for which variants have been shown to influence alcohol cue reactivity and brain activity in humans [84], as well as the AD risk-associated *DRD2* gene encoding the dopamine D2 receptor. We will augment this panel with SNPs in several other genes that have been shown to have pharmacogenetic treatment interactions with ethanol or medications to treat AUDs such as the *GABRA2* gene, *OPRM1*, *DBH*, and *GRIK1*. In each subject we will calculate a GRPS using the sum of the number of risk alleles (0,1,2) for each polymorphism in the panel. This genetic loading score can be used as a variable in the statistical models of treatment outcome. Before applying this in the ZNS samples, we will first explore and refine this approach in available "discovery" samples of over 1000 de-identified clinical trial subjects. Because the *SNCA* rs17015888 risk allele (G) has a relatively high frequency in both EAs and African Americans (AAs) (**~**.5 for both), we should be able to apply this method in a combined sample using AIMS to control for population genetic structure. Sensitivity analysis *in EAs only* (a separate analysis) will be performed. We expect that **~**75% of our sample (240 of 320) will be of EA descent.

Originally, for the first phase of the work we had planned to genotype subjects using a genome-wide chip in order to explore the use of these CFG derived GRPS to predict treatment outcomes and medication response in two available clinical trial samples of medication treatments for AUD (a sertraline and a topiramate trial) via patient level meta-analysis. However, a number of other available trials have been found to be available for genotyping, and since a larger study sample and *particularly a larger available sample of naltrexone treated subjects are available*, we have expanded the plan to include these additional samples. We anticipate having upwards of 900-1000 naltrexone (versus placebo) treated subjects with DNA samples and clinical trial data. Having this large core of naltrexone treated subjects should substantially increase our power to find naltrexone specific pharmacogenetic predictors. Additionally we can genotype other available samples including the zonisamide samples (currently about halfway thru trial) and the previously mentioned samples (topiramate, sertraline) and also those from trials of mecamylamine and Dutasteride, totaling about 1400 total DNA samples. We will explore using functional genomics methods, the ability to predict outcomes and medication response based on genotype and the use of combined genome-wide data. A similar but much more rudimentary method combinatory multi-gene approach has recently been used to improve response and remission rates in the treatment of major depression with antidepressants in a large (N~1200) prospective clinical trial. We will use multiple exploratory methods of data analysis to compare different algorithms and methods of predicting outcomes which will include more traditional methods of data analysis such as longitudinal mixed models, multilevel modeling, as well as newer approaches such as machine learning. The algorithms and methods of predicting response derived from these exploratory analyses can be further tested for predictive validity when the ongoing zonisamide trials (and potentially other ongoing medication clinical trials) are completed.

6.I. 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.J. STRESS REACTIVITY LAB PROCEDURES:

(Visit 2b)

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 4 hours long. A description of the procedure is provided in Table 3.

6.J.1. *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 six scripts for each subject (2 for each condition: stress, neutral, and alcohol) 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. Detailed procedures are outlined in the imagery development procedures manual.[86] Audiotapes will be destroyed after review. Due to the length of this appointment (4-6 hours), we will provide food for participants for the script development appointment.

6.J.2. *Manipulation Check for Script Development*: All six 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.,[87] and have been successfully used in previous work by co-investigators.

6.J.3. *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.[86] Relaxation training will be approximately 10 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. Participants will listen to one imagery recording for each condition (stress, neutral, and alcohol) at each lab. Each imagery recording will only be heard one time (the stress, neutral, and alcohol cues played during lab 1 will not be played during lab 2).

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.[86, 88] 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.J.4. 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. the length of the appointment; we will provide participants with food at the start of each lab session.

TABLE 3 Schedule for Stress Reactivity Laboratory Session Phase I, Day 4

T -20	Subject arrives; urine, BrAC check (≤ 0.02), CIWA, psychophysiological setup; BIS, STAI, BART, 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 minute 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

Table 3 Abbreviations: HR/BP: Heart rate/Blood pressure, BrAC: Breath Alcohol Concentration;

6.J.5. 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 [89]. 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.

Adverse Event Form (SAFTEE): In order to monitor adverse events from the study interventions, the SAFTEE will be administered before and after each session. This is a locally developed symptom checklist that includes possible side effects of study medications and/or procedures and has been used in our previous studies

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 1=”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)[94] 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.[94] The DES has been used to examine subjective emotion following laboratory mood inductions.[88]

Impulsivity will be assessed through the Balloon Analogue Risk Task (BART) [50]and Barrett Impulsivity Scale (BIS) [51]. 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[95, 96].

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 [97].

6.J.6. Physiological Measures: BP and HR will be assessed using an automatic blood pressure cuff.

6.K. Statistical Plan and Power Analysis:

6.K.1. Procedures: Procedures for the monitoring and analysis of data were developed during previous clinical trials conducted at Yale and will be overseen by Drs. Ralevski and Arias.

6.K.1.a. To Examine the Efficacy of ZNS (Specific Aim 1), Primary Outcome: We will use ***drinks per week*** as the primary outcome variable. This is also the primary outcome we are using for veteran ZNS study, and is one that can be readily applied when combining the samples. Recently the NIAAA and FDA Alcohol Clinical Trials Initiative (ACTIVE: a workgroup of experts in the field tasked with optimizing alcoholism clinical trials outcomes and methods) has suggested that for medication development trials and small to medium size trials, continuous outcome variables such as drinks/week or heavy drinking days per week are optimal as opposed to categorical outcomes. We will use a mixed models approach to examine for a statistically significant difference in drinks per week and on continuous secondary outcome variables. The model will include fixed effects for medication group, week, and the interaction between medication and week. We will include pre-treatment drinking behavior (past month HDD) as a covariate and will select the best-fitting variance-covariance structure based on Schwartz-Bayesian Information criterion (BIC). 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 last 8 weeks of treatment at the target dose. All of these outcomes can be obtained from the TLFB data, and from the daily drinking data obtained from the IVR.

An important initial consideration in considering efficacy will be to identify baseline differences between groups that may have occurred despite randomization. A successful outcome during the treatment trial will be defined in terms of a statistically significant difference on the primary outcome measure: drinks per week, compared during the 8 weeks of active treatment at the target dose, allowing for an 8 week grace period for the medication titration**.** For all analyses, heavy drinking days will be defined as follows; for men > 4 drinks in a day and for women > 3 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. All analyses will be **intent-to-treat**. The α will be set at .05 for the primary outcome variable. Between site differences will be explored. We will test interaction effects of GRPS in the regression models for the primary/secondary outcomes **(Exploratory Aim 1),** testing the hypothesis that ZNS's effect on drinking is greater in those with higher GRPS.

6.K.2 Secondary outcome measures: We will use a mixed models approach to examine for a statistically significant difference on heavy drinking days (HDD) per week, changes in GGTP level, measures of alcohol urge/craving (AUQ), and alcohol-related problems (as measured on the SIP). For each of these outcome measures, the model will include fixed effects for medication group, week, and the interaction between medication and week. We will include pre-treatment drinking behavior (past month HDD) as a covariate and will select the best-fitting variance-covariance structure based on Schwartz-Bayesian Information criterion (BIC). 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. We will use the Hommel's correction for multiple comparisons on the secondary outcomes to guard against chance findings. With last secondary outcome measure percentage of subjects with no heavy drinking days (PSNHDD), we will use a logistic regression analysis with PSNHDD as a categorical dependent variable. Medication condition (PLC or ZNS) will be the main independent variable, and we will include the variables of civilian or veteran status, and sex as covariates. We will also examine the use of biomarkers (GGT, PEth) to verify and adjust subjective drinking data as these biomarkers can detect occult harmful drinking when a subject is not forthcoming.

6. K. 3. Dropouts and missing data: For the analysis of PSNHDD using logistic regression, all dropouts will be counted as relapsed. For all repeated measures analysis, we will use all

available data on individuals and thus dropouts provide data until the point of dropout. 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 [98] to perform sensitivity analyses to our main analyses. Adherence to the medication will be evaluated and controlled for in secondary analyses. We will evaluate and compare both medication conditions (PLC, ZNS) for percentage of prescribed pills taken.

6. K. 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 Aim 2, Exploratory Aim 1): 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. [79], 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. [79], 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. K. 5. Stress Reactivity Lab (Exploratory Aim 2): *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.K. 6. Safety: Safety will be analyzed using categorical outcomes, defined by the type and severity of adverse effects. Summary measures of adverse events will be developed by organ system from the SAFTEE [77, 78] and will be compared for patients receiving ZNS or PLC using χ^2 analysis or Fisher's exact tests, with an emphasis on moderate-to-severe adverse events.

6. K. 7. Sample Size And Power Estimate (Specific Aim 1): For **continuous outcomes**, based on the effect sizes from our pilot study of ZNS (showing a moderate effect size on drinks/week d=0.5, and .27 HDD/week), we estimated that a study with **N=128** subjects (a 20% drop out rate) would be well powered (>.80) to detect a medium effect size difference on the secondary outcomes HDD per week and total drinks per week for the main effect of group assuming alpha level of 0.05. Based on past trials we are expecting a dropout rate < 30%. We will quantitatively examine the veteran and civilian populations for differences in variance and treatment response, and combine them (if valid) in a patient-level pooled analysis, further increasing power on all outcomes. If substantial differences are observed between the veteran and civilian samples, we will meta-analyze them. For **PSNHDD**, from the pilot study, in the ZNS group, 12 of 20 subjects did not relapse in the 28 days of the study, compared to 7 of 20 PLC subjects. Using this effect size, the proposed sample size of 80 subjects per group has >89% power to detect such a difference in the rates of no heavy drinking (i.e. 60% vs. 35%), assuming a two-sided alpha level of 0.05. We can also detect slightly smaller differences (60% vs. 38%, 35% vs. 57%) with 80% power under the same assumptions. Both in the estimation of effect

size from the pilot data and in the sample size analysis, dropouts are counted as relapsed to heavy drinking.

6 K. 8. Pharmacogenomic and Micro-longitudinal analyses power estimate (Aim 2, exploratory aims): There is little ZNS-specific data by which we could reasonably estimate effect sizes for these analyses. Three recent treatment studies by our group showed significant pharmacogenetic effects with samples of about 110-150 in each [15, 85, 102]. By using a mixed models approach on drinking variables, and HLM for the micro-longitudinal analyses, we will be adequately powered to detect medium-to-large effects in these analyses.

6.L. Economic Considerations: Participants will be paid a nominal but fair amount of money for their time and participation, up to *$1110* (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 4).

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 $1110 (this does not include the additional travel compensation mentioned earlier). This payment is for the time and effort associated with study assessments and procedures. All payments will be in the form of cash, check, gift card or clin card, upon completion of each appointment.

TABLE 4: Subject visit and payment overview:

Visit title	VISIT #	Weeks of completed medication	Payment ($)
Screening	1		50
Baseline	2	0	65
Weekly treatment visit	3	1	25
Biweekly treatment visit	4	3	40
Biweekly treatment visit	5	5	40
Biweekly treatment visit TARGET DOSE achieved (500mg)	6	7	40
Biweekly treatment visit- **midpoint assessments**. Subjects eligible to go to 600mg daily.	7	9	45
Biweekly treatment visit	8	11	40
Biweekly treatment visit	9	13	40
Endpoint visit	10	16	80
Two weeks post endpoint visit follow up (end of medication taper)	11		15
3 month follow up visit	12		30
Total	**12**		**510**

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 ($2 per completed phone call plus $6 for each week where 6 or more calls are completed (up to $20/week for 16 weeks))
Maximum Total compensation for all visits, labs, and phone calls			**1110**

FOR ADDITIONAL DETAILS OF SAFETY AND HUMAN SUBJECTS PROTECTION, PLEASE REFER TO THE ATTACHED "HUMAN SUBJECTS" APPENDIX FROM THE GRANT. ALSO, WE HAVE ATTACHED THE CORRESPONDING GRANT APPLICATION FOR MORE INFORMATION.

7. **Data and Safety Monitoring Board**

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. The DSMB for this study had been composed of three investigators located in Connecticut (at Yale) 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 three are directly involved with this proposed trial and consequently should not pose a conflict of interest. All are faculty at Yale. DSMB members have been transitioned to a VCU faculty composed board and members include Drs. Yifrah Kaminer, Megan S. Lemay and Gaurav Gupta, who are not directly involved in this trail. These clinicians have appropriate expertise in clinical trials and with expertise in substance abuse and psychopharmacology.

Review will occur every 6 months. The DSMB will review any serious and unanticipated events, also severe adverse events and patterns. Additional items may be review like issues with dropouts or early terminations, data issues.

TABLE 5: Abbreviations:

AADUD	Alcohol Dependence Use Disorder – Measures effects of alcohol on life using DSM V criteria
AEQ	Alcohol Expectations Questionnaire - Measure of number of drinks subjects report are needed to produce typical alcohol effects (alcohol sensitivity)
AUQ	Alcohol Urge Questionnaire – Assesses alcohol cravings
BART	Balloon Analogue Risk Task- Assesses reward vs loss to assess risk-taking behavior
BIS	Barratt Impulsiveness Scale -Impulsivity Scale- self-reported measures of impulsive personality traits
BLT	Brown Location Test - Visual learning task independent of verbal, global intellectual, fine motor or drawing skills that consists of five recall learning trials, an interference trial, and a short delay recall
CAPS-5	Clinician Administered PTSD Scale for DSM-5 – Measures symptoms of PTSD
CGI-I	Clinical Global Impression – improvement – Assesses for improvement in baseline since initiation
CGI-S	Clinical Global Impression – severity – To rate severity of patient mental illness
CIWA	Clinical Institute Withdrawal Assessment - Assesses for symptoms of withdrawal
C-SSRS	Columbia Suicide Severity Rating Scale – Suicidal ideation and behavior rating scale
DMQ	Drinking Motives Questionnaire – Assesses personal motives for drinking alcohol
FHAM	Family History Assessment Model – Assesses for psychiatric disorders among relatives of participant
IVR	Interactive Voice Response – A phone system used for self-reporting predetermined questions
LSCR	Lifetime Stressor Checklist – Revised - Self-report measure that assesses traumatic or stressful life events
MM	Medical Management- A method of conducting a patient visit based on a theoretical paradigm to evaluate adherence to medications and adherence to treatment
MED-Q	Medication Questionnaire- Assesses the participant's belief as to their treatment condition
PCL-5	PTSD Checklist for DSM 5 – Assesses for presence of PTSD symptoms
PHQ-9	Physician's Health Questionnaire - 9-item self-report measure of depressive symptoms with a total score of 0-27
PSS	Perceived Stress Scale - Ten item scale measuring perceived stress
Q-LES-Q	Quality of Life Enjoyment and Satsfaction Questionnaire - Assesses quality of life in subjects
RAND SF-12	RAND (Research AND development) 12 Item Short Form Health Survey – Assesses personal habits and views on personal health
SAFTEE	Systematic Assessment for Treatment of Emergent Effects - Measure of adverse events

SCID Section E	Structured Clinical Interview - Assesses for substance abuse disorders according to DSM V
SCID-II (antisocial)	Structured Clinical Interview - Assesses **Conduct Disorder and Antisocial Personality Disorder Criteria**
SCID V	Structured Clinical Interview - Classifies patients according to the presence or absence of standard psychiatric disorders according to DSM-5 criteria
SIP	Short Inventory of Problems – Evaluates experiences of drinkers over past 3 months
SLEI	Stressful Life Event Inventory – Evaluation of stressful life event occurrences over the past month
SORT	Slosson Oral Reading Test- evaluates English reading level
SRE	Self Rating Effects of Alcohol – Self-reported numeric responses to number of drinks needed to achieve certain effects
STAI	State-Trait anxiety Inventory - Measures state and anxiety level
TIPI	Ten item personality inventory – Assesses personality traits
TLFB	Timeline Follow-back- Estimates past 90-day drinking

REFERENCES

1. Harwood, H., *Updating Estimates of the Economic Costs of Alcohol Abuse in the United States: Estimates, Update Methods, and Data. Report prepared by The Lewin Group for the National Institute on Alcohol Abuse and Alcoholism*, NIAAA, Editor. 2000, NIAAA: Rockville Maryland.
2. Hasin, D.S., et al., *Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions.* Arch Gen Psychiatry, 2007. **64**(7): p. 830-42.
3. Mokdad, A.H., et al., *Actual causes of death in the United States, 2000.* JAMA : the journal of the American Medical Association, 2004. **291**(10): p. 1238-45.
4. Johnson, B.A., *Update on neuropharmacological treatments for alcoholism: scientific basis and clinical findings.* Biochemical pharmacology, 2008. **75**(1): p. 34-56.
5. Cohen, E., et al., *Alcohol treatment utilization: findings from the National Epidemiologic Survey on Alcohol and Related Conditions.* Drug and alcohol dependence, 2007. **86**(2-3): p. 214-21.
6. Mark, T.L., et al., *Barriers to the use of medications to treat alcoholism.* The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions, 2003. **12**(4): p. 281-94.
7. Gadde, K.M., et al., *Zonisamide for weight loss in obese adults: a randomized controlled trial.* JAMA : the journal of the American Medical Association, 2003. **289**(14): p. 1820-5.
8. McElroy, S.L., et al., *Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial.* J Clin Psychiatry, 2006. **67**(12): p. 1897-906.
9. Mueller, T.I., et al., *A double-blind, placebo-controlled pilot study of carbamazepine for the treatment of alcohol dependence.* Alcohol Clin Exp Res, 1997. **21**(1): p. 86-92.
10. Brady, K.T., et al., *The use of divalproex in alcohol relapse prevention: a pilot study.* Drug and alcohol dependence, 2002. **67**(3): p. 323-30.

11. Johnson, B.A., et al., *Oral topiramate for treatment of alcohol dependence: a randomised controlled trial.* Lancet, 2003. **361**(9370): p. 1677-85.
12. Johnson, B.A., et al., *Topiramate for treating alcohol dependence: a randomized controlled trial.* JAMA : the journal of the American Medical Association, 2007. **298**(14): p. 1641-51.
13. Spaeth, G.L. and A.V. Mantravadi, *Topiramate as treatment for alcohol dependence.* JAMA : the journal of the American Medical Association, 2008. **299**(4): p. 405; author reply 406-7.
14. Stringer, S., M. Rueve, and D. Mossman, *Topiramate as treatment for alcohol dependence.* JAMA : the journal of the American Medical Association, 2008. **299**(4): p. 405-6; author reply 406-7.
15. Kranzler, H.R., et al., *Topiramate Treatment for Heavy Drinkers: Moderation by a GRIK1 Polymorphism.* Am J Psychiatry, 2014.
16. Mason, B.J., et al., *Gabapentin treatment for alcohol dependence: a randomized clinical trial.* JAMA Intern Med, 2014. **174**(1): p. 70-7.
17. Knapp, C.M., et al., *Zonisamide decreases ethanol intake in rats and mice.* Pharmacol Biochem Behav, 2007. **87**(1): p. 65-72.
18. Arias, A.J., et al., *Placebo-controlled trial of zonisamide for the treatment of alcohol dependence.* Journal of Clinical Psychopharmacology, 2010. **30**(3): p. 318-22.
19. Knapp, C.M., et al., *Open label trial of the tolerability and efficacy of zonisamide in the treatment of alcohol dependence.* The American journal of drug and alcohol abuse, 2010. **36**(2): p. 102-5.
20. Rubio, G., et al., *Effects of zonisamide in the treatment of alcohol dependence.* Clinical neuropharmacology, 2010. **33**(5): p. 250-3.
21. Sarid-Segal, O., et al., *The anticonvulsant zonisamide reduces ethanol self-administration by risky drinkers.* The American journal of drug and alcohol abuse, 2009. **35**(5): p. 316-9.
22. Rubio, G., et al., *Zonisamide versus diazepam in the treatment of alcohol withdrawal syndrome.* Pharmacopsychiatry, 2010. **43**(7): p. 257-62.
23. Knapp, C.M., et al., *Zonisamide, topiramate, and levetiracetam: efficacy and neuropsychological effects in alcohol use disorders.* J Clin Psychopharmacol, 2015. **35**(1): p. 34-42.
24. White, H.S., *Mechanism of action of newer anticonvulsants.* J Clin Psychiatry, 2003. **64 Suppl 8**: p. 5-8.
25. Ueda, Y., et al., *Effect of zonisamide on molecular regulation of glutamate and GABA transporter proteins during epileptogenesis in rats with hippocampal seizures.* Brain Res Mol Brain Res, 2003. **116**(1-2): p. 1-6.
26. Yoshida, S., et al., *Effects of zonisamide on neurotransmitter exocytosis associated with ryanodine receptors.* Epilepsy research, 2005. **67**(3): p. 153-62.
27. Kim, J.H., et al., *Effects of chronic exposure to ethanol on glutamate transporter EAAT3 expressed in Xenopus oocytes: evidence for protein kinase C involvement.* Alcohol Clin Exp Res, 2005. **29**(11): p. 2046-52.
28. Kinrys, G., D. Vasconcelos e Sa, and F. Nery, *Adjunctive zonisamide for treatment refractory anxiety.* Int J Clin Pract, 2007. **61**(6): p. 1050-3.
29. Mula, M., S. Pini, and G.B. Cassano, *The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence.* J Clin Psychopharmacol, 2007. **27**(3): p. 263-72.
30. Asanuma, M., et al., *Neuroprotective effects of zonisamide target astrocyte.* Annals of neurology, 2010. **67**(2): p. 239-49.
31. Sonsalla, P.K., et al., *The antiepileptic drug zonisamide inhibits MAO-B and attenuates MPTP toxicity in mice: clinical relevance.* Experimental neurology, 2010. **221**(2): p. 329-34.
32. Okada, M., et al., *Biphasic effects of zonisamide on serotonergic system in rat hippocampus.* Epilepsy research, 1999. **34**(2-3): p. 187-97.

33. Okada, M., et al., *Effects of zonisamide on dopaminergic system.* Epilepsy research, 1995. **22**(3): p. 193-205.
34. DRUGDEX, *Zonisamide. In:*. Updated Periodically, Thompson Healthcare: Greenwood Village, Colo.
35. Eisai, *Zonegran (Zonisamide) Official Product Labeling*. 2009, FDA: Woodcliff Lake, NJ.
36. Wilfong, A.A. and L.J. Willmore, *Zonisamide - a review of experience and use in partial seizures.* Neuropsychiatr Dis Treat, 2006. **2**(3): p. 269-80.
37. Gadde, K.M., et al., *Zonisamide for Weight Reduction in Obese Adults: A 1-Year Randomized Controlled Trial.* Arch Intern Med, 2012: p. 1-8.
38. McElroy, S.L., et al., *Zonisamide in the treatment of binge-eating disorder: an open-label, prospective trial.* J Clin Psychiatry, 2004. **65**(1): p. 50-6.
39. Tonstad, S., et al., *Efficacy and safety of topiramate in the treatment of obese subjects with essential hypertension.* Am J Cardiol, 2005. **96**(2): p. 243-51.
40. McElroy, S.L., et al., *Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial.* Am J Psychiatry, 2003. **160**(2): p. 255-61.
41. McElroy, S.L., et al., *Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study.* Biol Psychiatry, 2007. **61**(9): p. 1039-48.
42. McElroy, S.L., et al., *Topiramate in the long-term treatment of binge-eating disorder associated with obesity.* J Clin Psychiatry, 2004. **65**(11): p. 1463-9.
43. Drake, M.E., Jr., et al., *Open-label zonisamide for refractory migraine.* Clin Neuropharmacol, 2004. **27**(6): p. 278-80.
44. Sackellares, J.C., et al., *Pilot study of zonisamide (1,2-benzisoxazole-3-methanesulfonamide) in patients with refractory partial seizures.* Epilepsia, 1985. **26**(3): p. 206-11.
45. Kranzler, H.R., et al., *Self-efficacy mediates the effects of topiramate and GRIK1 genotype on drinking.* Addict Biol, 2014.
46. Levey, D.F., et al., *Genetic risk prediction and neurobiological understanding of alcoholism.* Transl Psychiatry, 2014. **4**: p. e391.
47. Pettinati, H.M. and National Institute on Alcohol Abuse and Alcoholism (U.S.), *Medical management treatment manual : a clinical research guide for medically trained clinicians providing pharmacotherapy as part of the treatmemt for alcohol dependence*. COMBINE monograph series. 2004, Bethesda, MD: U.S. Dept. of Health and Human Services, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism.
48. Sinha, R., *How does stress lead to risk of alcohol relapse?* Alcohol Res, 2012. **34**(4): p. 432-40.
49.
50. Lejuez, C.W., et al., *Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART).* J Exp Psychol Appl, 2002. **8**(2): p. 75-84.
51. Patton, J.H., M.S. Stanford, and E.S. Barratt, *Factor structure of the Barratt impulsiveness scale.* J Clin Psychol, 1995. **51**(6): p. 768-74.
52. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.
53. First, M.B., Williams, Janet B.W., Spitzer, Robert L., and Gibbon, Miriam, *Structured Clinical Interview for DSM-5 Axis I Disorders, Clinical Trials Version (SCID-CT).* 2014, New York, NY: American Psychiatric Press Inc.
54. Rice, J.P., et al., *Comparison of direct interview and family history diagnoses of alcohol dependence.* Alcohol Clin Exp Res, 1995. **19**(4): p. 1018-23.
55. Sobell, L.C. and M.B. Sobell, *Timeline Follow-Back - a Technique for Assessing Self-Reported Alcohol-Consumption.* Measuring Alcohol Consumption, 1992: p. 41-72.
56. Carney, M.A., et al., *Levels and patterns of alcohol consumption using timeline follow-back, daily diaries and real-time "electronic interviews".* Journal of studies on alcohol, 1998. **59**(4): p. 447-54.

57. Searles, J.S., J.E. Helzer, and D.E. Walter, *Comparison of drinking patterns measured by daily reports and timeline follow back.* Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors, 2000. **14**(3): p. 277-86.
58. Bohn, M.J., D.D. Krahn, and B.A. Staehler, *Development and initial validation of a measure of drinking urges in abstinent alcoholics.* Alcohol Clin Exp Res, 1995. **19**(3): p. 600-6.
59. Feinn, R., H. Tennen, and H.R. Kranzler, *Psychometric properties of the short index of problems as a measure of recent alcohol-related problems.* Alcohol Clin Exp Res, 2003. **27**(9): p. 1436-41.
60. Endicott, J., et al., *Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure.* Psychopharmacol Bull, 1993. **29**(2): p. 321-6.
61. Cooper, M.L., *Motivations for alcohol use among adolescents: Development and validation of a four-factor model.* Psychological assessment, 1994. **6**(2): p. 117.
62. Cooper, M.L., et al., *Stress and alcohol use: moderating effects of gender, coping, and alcohol expectancies.* J Abnorm Psychol, 1992. **101**(1): p. 139-52.
63. George, W.H., et al., *A revised Alcohol Expectancy Questionnaire: factor structure confirmation, and invariance in a general population sample.* J Stud Alcohol, 1995. **56**(2): p. 177-85.
64. Schuckit, M.A., T.L. Smith, and J.E. Tipp, *The Self-Rating of the Effects of alcohol (SRE) form as a retrospective measure of the risk for alcoholism.* Addiction, 1997. **92**(8): p. 979-88.
65. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure.* J Gen Intern Med, 2001. **16**(9): p. 606-13.
66. Ware, J., Jr., M. Kosinski, and S.D. Keller, *A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity.* Med Care, 1996. **34**(3): p. 220-33.
67. Spielberger, C.D.G., R L (*Manual for the State-trait anxiety inventory (form Y) ("self-evaluation questionnaire")*. 1983, Palo Alto, CA: Consulting Psychologists Press.
68. Posner, K., et al., *The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults.* Am J Psychiatry, 2011. **168**(12): p. 1266-77.
69. Cohen, S., T. Kamarck, and R. Mermelstein, *A global measure of perceived stress.* J Health Soc Behav, 1983. **24**(4): p. 385-96.
70. Weathers, F.W., D.D. Blake, and P.P. Schnurr, *Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). US Department of Veterans Affairs. PTSD: National Center for PTSD. Professional*. 2015.
71. Weathers, F.W., et al., *The ptsd checklist for dsm-5 (pcl-5).* Scale available from the National Center for PTSD at www. ptsd. va. gov, 2013.
72. Brown, F.C., et al., *A new measure of visual location learning and memory: development and psychometric properties for the Brown Location Test (BLT).* Clin Neuropsychol, 2007. **21**(5): p. 811-25.
73. Brown, F.C., et al., *Visual memory in patients after anterior right temporal lobectomy and adult normative data for the Brown Location Test.* Epilepsy Behav, 2010. **17**(2): p. 215-20.
74. Tombaugh, T.N., *Trail Making Test A and B: normative data stratified by age and education.* Arch Clin Neuropsychol, 2004. **19**(2): p. 203-14.
75. Tombaugh, T.N., J. Kozak, and L. Rees, *Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming.* Arch Clin Neuropsychol, 1999. **14**(2): p. 167-77.
76. Van der Elst, W., et al., *Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation.* J Int Neuropsychol Soc, 2005. **11**(3): p. 290-302.
77. Levine, J. and N.R. Schooler, *SAFTEE: a technique for the systematic assessment of side effects in clinical trials.* Psychopharmacol Bull, 1986. **22**(2): p. 343-81.

78. Johnson, B.A., N. Ait-Daoud, and J.D. Roache, *The COMBINE SAFTEE: a structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field.* J Stud Alcohol Suppl, 2005(15): p. 157-67; discussion 140.
79. Kranzler, H.R., et al., *Variation in OPRM1 moderates the effect of desire to drink on subsequent drinking and its attenuation by naltrexone treatment.* Addict Biol, 2013. **18**(1): p. 193-201.
80. Kranzler, H.R., et al., *5-HTTLPR genotype and daily negative mood moderate the effects of sertraline on drinking intensity.* Addict Biol, 2013. **18**(6): p. 1024-31.
81. Kranzler, H.R., et al., *Using daily interactive voice response technology to measure drinking and related behaviors in a pharmacotherapy study.* Alcohol Clin Exp Res, 2004. **28**(7): p. 1060-4.
82. Feinn, R., et al., *Measurement and prediction of medication compliance in problem drinkers.* Alcohol Clin Exp Res, 2003. **27**(8): p. 1286-92.
83. Kosoy, R., et al., *Ancestry informative marker sets for determining continental origin and admixture proportions in common populations in America.* Hum Mutat, 2009. **30**(1): p. 69-78.
84. Wilcox, C.E., et al., *Genetic variation in the alpha synuclein gene (SNCA) is associated with BOLD response to alcohol cues.* J Stud Alcohol Drugs, 2013. **74**(2): p. 233-44.
85. Kranzler, H.R., et al., *A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset [corrected] and 5-hydroxytryptamine transporter-linked promoter region genotype.* Journal of clinical psychopharmacology, 2011. **31**(1): p. 22-30.
86. Sinha, R., *"Manual for imagery script development procedures."* 2001.
87. Miller, G.A., D.N. Levin, M.J. Kozak, E.W.I. Cook, A. McLean, Jr., and P.J. Lang, *Individual differences in imagery and the psychophysiology of emotion. .* Cognition & Emotion, 1987. **1**: p. 367-390.
88. Sinha, R., D. Catapano, and S. O'Malley, *Stress-induced craving and stress response in cocaine dependent individuals.* Psychopharmacology (Berl), 1999. **142**(4): p. 343-51.
89. Watson, D., L.A. Clark, and A. Tellegen, *Development and validation of brief measures of positive and negative affect: the PANAS scales.* J Pers Soc Psychol, 1988. **54**(6): p. 1063-70.
90. McNair, D., M. Lorr, and L. Dropperman, *Manual for profile of mood states*. 1971, San Diego, CA: Educational and industrial testing services.
91. Fischman, M.W. and R.W. Foltin, *Utility of subjective-effects measurements in assessing abuse liability of drugs in humans.* Br J Addict, 1991. **86**(12): p. 1563-70.
92. de Wit, H. and R.R. Griffiths, *Testing the abuse liability of anxiolytic and hypnotic drugs in humans.* Drug Alcohol Depend, 1991. **28**(1): p. 83-111.
93. Levin, E.D., et al., *Transdermal nicotine effects on attention.* Psychopharmacology (Berl), 1998. **140**(2): p. 135-41.
94. Izard, C., *Patterns of emotions: A new analysis of anxiety and depression. .* 1972, San Diego, CA: Academic Press.
95. Sofuoglu, M., et al., *Riluzole and D-amphetamine interactions in humans.* Prog Neuropsychopharmacol Biol Psychiatry, 2008. **32**(1): p. 16-22.
96. Weafer, J. and M.T. Fillmore, *Comparison of alcohol impairment of behavioral and attentional inhibition.* Drug Alcohol Depend, 2012. **126**(1-2): p. 176-82.
97. Spielberger, C.D., et al., *Manual for the state-trait anxiety inventory (form Y): self-evaluation questionnaire*. 1983: Consulting Psychologists Press Palo Alto, CA.
98. Hedeker, D. and R. Gibbons, *Application of random-effects pattern-mixture models for missing data in longitudinal studies.* Psychological Methods, 1997. **2**(1): p. 64-78.
99. Walls, T.A. and J.L. Schafer, *Models for intensive longitudinal data*. 2006, Oxford ; New York: Oxford University Press. xxii, 288 p.
100. Kraemer, H.C., et al., *Mediators and moderators of treatment effects in randomized clinical trials.* Arch Gen Psychiatry, 2002. **59**(10): p. 877-83.

101. Kraemer, H.C., et al., *How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors.* Am J Psychiatry, 2001. **158**(6): p. 848-56.
102. Arias, A.J., et al., *Pharmacogenetics of naltrexone and disulfiram in alcohol dependent, dually diagnosed veterans.* Am J Addict, 2014. **23**(3): p. 288-93.