Title: Open Label Pilot Study of Perampanel for the Treatment of Alcohol Use Disorder

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Open Label Pilot Study of Perampanel for the Treatment of Alcohol Use Disorder
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SPECIFIC AIMS: Better medications to treat Alcohol Use Disorder (AUD) are greatly needed. Existing treatments are very limited in their effects, and are often not well adhered to or tolerated by patients. Pre-clinical studies show that activation of glutamatergic AMPA receptors (AMPA-Rs) promotes the return to drug and alcohol seeking behavior in mammals. Thus AMPA-R antagonist medications like perampanel, a recently FDA approved anticonvulsant, have clear potential in treating AUD, a fact which is supported by additional preclinical studies in animals. Though several glutamatergic medications have shown efficacy in treating AUD, selective AMPA- R antagonists remain unexplored in the treatment literature.

Perampanel administration was perceived as pleasing by subjects in one study, suggesting that it may be more acceptable to patients, and thus better adhered to, than current treatments are. Furthermore, perampanel could be a potential treatment for co-occurring anxiety disorders (e.g., posttraumatic stress disorder) and other addictive disorders (e.g., cocaine dependence). While we suspect perampanel has strong anti-alcohol addiction properties by itself, we plan to also explore combining perampanel with disulfiram, an FDA approved treatment for AUD which is poorly adhered to, thus making a multi-faceted (multi-mechanism of action) approach to reducing drinking. We predict that perampanel will reduce drinking by reducing the rewarding and reinforcing properties of alcohol. Disulfiram has an aversive effect making people physically ill when they drink alcohol. We suspect that by combining the two medications we will have a highly effective treatment for AUD, and one which is analogous to buprenorphine in the treatment of opioid use disorder in that it reduces anxiety, craving, and the motivation to drink, and once ingested it essentially blocks the ability to drink (due to the disulfiram-ethanol reaction).

Specific Aim 1: To test the efficacy of perampanel treatment of AUD in a small, open-label, eight-week, quasi-experimental clinical trial in which 20 subjects with AUD will be randomized 1:1 to one of two groups; perampanel by itself, and perampanel combined with disulfiram. Subjects will be titrated over 3 weeks to a target dose of 8mg perampanel daily in both groups, and disulfiram will be kept at 250mg daily. Subjects will be compared on the primary outcome of percent abstinent days, in quasi-experimental fashion to 20 placebo treated subjects from our existing clinical trial databases. *We hypothesize that perampanel will reduce drinking and craving significantly more than placebo, and that the combined perampanel/disulfiram group will reduce drinking the most, with no difference in adherence compared to perampanel without disulfiram*. Drinking data measurement and safety efforts will be augmented with twice-daily breathalyzer measurements collected with a smartphone-based monitoring platform and relayed to investigators daily.

A. BACKGROUND AND SIGNIFICANCE: Pre-clinical studies show that activation of glutamatergic AMPA receptors (AMPA-Rs) promotes the return to drug and alcohol-seeking behavior in mammals. AMPA receptor (AMPA-R) antagonist (i.e., blocking) medications such as perampanel, a recently FDA approved anticonvulsant, may be useful in treating alcohol use disorder (AUD). The main goal of the proposed study is to determine if perampanel reduces drinking in a small, open-label, pilot study, it would provide a strong rationale for further clinical trials with this medication.

A.1. Critical need for new AUD treatments: There is a great need to develop more effective medications to treat AUD. AUD is among the most prevalent and disabling disorders in the world, with an estimated impact of $185 billion in the U.S. annually, and is the third leading preventable cause of death (1-3). The currently available medications to treat AUD have modest

effects, and many patients don't respond well, thus there is a need for more efficacious pharmacologic treatments (4, 5).

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 (6, 7). 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 (7). Perampanel may be better tolerated than some other available treatments for reducing drinking such as topiramate. The study by Mark et al. (7) 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 perampanel's effects on the rewarding and reinforcing properties of alcohol. We will also generate critical pilot clinical trial data.*

A.2. Treating AUDs with Anticonvulsants: Anticonvulsants have shown evidence of efficacy in treating alcoholism (8). Perampanel is an anticonvulsant and a promising potential treatment for AUD. 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 placebo 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 placebo 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. The frequency and severity of side effects from topiramate limit its effectiveness (12-14).

A.3. Glutamate and Addiction: Altered glutamatergic neurotransmission plays a prominent role in the pathophysiology of AUD (15, 16). Glutamatergic neurotransmission within and on brain dopaminergic pathways is thought to be a key and necessary component for the development and maintenance of addiction to alcohol (17). Glutamatergic efferents from the prefrontal cortex (PFC), amygdala, and hippocampus, innervate the cell bodies of neurons in the ventral tegmental area (VTA) and the nucleus accumbens shell (NAS), facilitating dopaminergic transmission in these key areas of the "reward pathway" (17).

A.4. AMPA Receptors and AUD Pathophysiology: Glutamate acts on N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxyl-5-methyl-isoxazole-4-proprionic acid (AMPA), kainite, and metabotropic receptors. AMPA-Rs may have a more significant role than other glutamatergic receptors in glutamate-facilitated dopamine release in the NAS and subsequent reward. AMPA-Rs play a prominent role in addiction related neuroplasticity and learned behaviors. Glutamatergic activation of VTA dopaminergic neurons and subsequent dopamine release in the NAS is important in addiction to any substance, but activation of AMPA-Rs pre-synaptically in the NAS, and also activation of AMPA-Rs in the PFC further potentiates dopaminergic neurotransmission (and thus reward and reinforcement) in the NAS. Infusion of an NMDA antagonist into the NAS of rats does not block cocaine-induced relapse to cocaine self-administration, but infusion into the NAS of an AMPA-R antagonist does (17, 18). AMPA-R antagonists may reduce the reward and reinforcement of alcohol and other drugs and may reduce craving and relapse risk. More recent animal studies have confirmed these previous findings and suggest that AMPA-Rs are involved in the return to drug seeking behavior (19-24).

AMPA-R antagonists injected into the Nucleus Accumbens Core (NAC) attenuate cue-induced relapse to cocaine (25). Sanchis-Segura et al., (26) showed the AMPA-R antagonist GYKI 52466 reduced cue-elicited reinstatement of alcohol seeking behavior and the alcohol deprivation effect in two animal models. An AMPA-R antagonist injected into the NA reduced conditioned place aversion from naloxone in rats (27). A very recent study in rats confirmed the theory that enhanced AMPA-R mediated glutamatergic transmission due to neuroadaptation from chronic alcohol exposure is a main component of the drive to drink excessively and to

crave alcohol after being exposed to cues (28). In that study, an AMPA-R **agonist** increased ethanol consumption in a self-administration paradigm, as well as cue-elicited relapse in alcohol preferring rats; an effect that was blocked by an AMPA-R **antagonist** (like perampanel). These studies strongly support perampanel as a good candidate for alcoholism treatment.

Additional support for the critical role of the AMPA receptor in AUD pathophysiology comes from genetic studies of AUD, which emphasize the network of genes related to trafficking of the AMPA-R as a component of addiction-related neuroplasticity. Karpyak et al., (29) examined variants in the genes encoding proteins in this so-called "NMDA dependent AMPA receptor trafficking cascade" in association to alcoholism in humans. They studied a set of ~1000 single nucleotide polymorphisms (SNPs) in 13 genes related to the pathway, finding via gene set analysis that the set was significantly associated with AUD. Further, some of the most significantly associated SNPs were located in genes responsible for encoding subunits of AMPA receptors, specifically *GRIA2A*, *GRIA3*, and *GRIA4*. Meyers et al., (30) studied genetic variants in the mGluR–eEF2–AMPAR pathway in association to alcohol drinking behaviors in humans. They found that 206 genetic variants across the same pathway (including ones in the *GRIA1* and *GRIA4* genes) were found to predict number of drinking days per month (corrected *P*-value <0.01) when considered as a set. They were able to replicate the finding to some degree in another sample, where variants in two of the genes seemed to be predictive of amount of alcohol consumed. This genetic work strengthens the evidence base linking AMPA-R related glutamatergic neurotransmission to AUD pathophysiology.

A.5. Perampanel Pharmacology: Perampanel is a noncompetitive (allosteric) antagonist of the AMPA-R that is well-absorbed (100% bioavailability), has good blood-brain-barrier penetration, and rapidly reaches peak plasma concentrations (1 hour) (31). Perampanel is now FDA approved for the adjunctive treatment of refractory partial-onset seizures. Phase III trials in epilepsy have demonstrated that perampanel is very well tolerated, and safe (32-34). In vitro studies of rat hippocampal slices have demonstrated the selective action of perampanel on the AMPA receptor (35). Perampanel does not appear to block the ion channel, but binds the AMPA-R at an allosteric site referred to as the "GYKI receptor" (35, 36). In human subjects, perampanel is well tolerated at doses of 8mg or 12mg daily, although some titration is needed to reach those doses for ongoing therapy (33, 34, 37). Medication related adverse events/side effects with chronic dosing in epilepsy trials have included; dizziness, somnolence, irritability, headache, fall, and ataxia (33, 34, 37). Pharmacokinetically, perampanel has an elimination half-life $T_{1/2}$ of over 52 hours (estimated at average ~70 hours, but with a wide inter-individual range from 52-129 hours) and reaches peak plasma concentration (T_{max}) approximately 1 hours post-ingestion (31). Perampanel is primarily metabolized by CYP3A4 and exhibits linear pharmacokinetics. To date, there have been no clinical trials of AMPA-R antagonists (e.g., perampanel) for the treatment of alcoholism.

Perampanel is a DEA schedule III drug, owing to a study that showed that very high doses of perampanel (i.e., 2-3 times the maximum recommended dose) caused some euphoria and drug liking similar to alprazolam and ketamine (38). However at normal doses (and the ones we will use here in this study) that effect did not occur. We anticipate that at normal doses, perampanel will produce a pleasant mood, reduction in anxiety, and decrease in the drive to drink alcohol. This is important, because the currently FDA approved medications for AUD do not really have any effect on mood or anxiety. We think that alcoholics will want to take perampanel because they will feel "normal" again, and like they don't need to drink. Perampanel will have the stabilizing good effects that they sought out of alcohol, but without the negative effects, and it will decrease the desire for alcohol as well as its other reinforcing effects Disulfiram ingestion makes it impossible to drink alcohol without getting physically ill (i.e., the disulfiram reaction), however disulfiram lacks efficacy in treating AUD under normal treatment conditions because patients stop taking it. Combining perampanel with disulfiram would give AUD patients the feeling that they don't need to drink, along with a deterrent from drinking. Thus the role of the combination drug in AUD treatment would be somewhat analogous to that of buprenorphine treatment in opioid use disorder treatment; it would make patients feel like they

don't need to drink, and would make it impossible to get drunk while on it. We envision that it would be used for a limited amount of time, perhaps 3-6 months, under close medical supervision, to help patients gain some sobriety and work on their recovery. In our study, diversion and inappropriate use will be thwarted by issuing only a one-week supply of medication at any one time. We envision that eventually perampanel will be used for the treatment of AUD as a combination of disulfiram and perampanel mixed together (compounded) in one pill, hence stability testing for this combination is in development for future protocols. Note that modafinil and buprenorphine are both controlled substances, but both are efficacious medications in treating opioid and cocaine addiction. We don't have an AUD treatment that is as effective as buprenorphine for opioid use disorder, but one is needed.

A.6. A Precision-Medicine approach for treating AUD: Pharmacogenetic studies of alcoholism to date suggest that we may be able to guide treatment selection based on variation in a patient's genes (39, 40). Glutamatergic neurotransmission genes have been implicated in numerous studies. Karpyak et al. (41) found that variation in glutamateric genes were associated to difference in length of time that AUD subjects were able to maintain abstinence from alcohol during treatment with acamprosate. Also, recently, a study of variation in metabolism of many key biological compounds showed that subjects with AUD that had increased serum glutamate levels responded better to the medication acamprosate in treatment (42).

B. METHODS:

OVERVIEW: Testing the efficacy of perampanel treatment of AUD in a small, open-label, trial. Twenty (**N=20**) treatment seeking subjects with DSM-5 AUD that are currently heavy drinking regularly will be randomized (1:1) to two non-blinded conditions; perampanel by itself, or perampanel in combination with disulfiram. All subjects will take the Perampanel for **eight weeks**, with a three-week titration, increasing 2mg weekly, to a target dose of 8mg daily that they will take for 5 weeks (table 2). Subjects who are randomized to also receive Disulfiram with Perampenel for eight weeks, will receive a combination liquid, to also include a disulfiram three-week titration, increasing weekly to a target dose of 250mg daily (table 2). . Subjects will be seen weekly and data on drinking will be collected with the timeline follow-back method (**TLFB)** (43). Craving will be measured with the **AUQ** weekly. To monitor for diversion, and reduce the risk of taking more than prescribed amount of medication, subjects will only be dispensed a 1-week supply of medication at any visit. Subjects will also be called mid-week in between visits to assess for any severe psychiatric side effects, and so they will be queried twice weekly for any suicidal or homicidal ideation. Subjects will be tapered off the medication over two weeks at the end of the study and followed closely during that time to assess side effects. Subjects will also be monitored daily with the "Soberlink" breath alcohol monitoring system, which is a smartphone-based system that transmits twice daily breathalyzer measurements to researchers. It automatically notifies researchers if there is a positive measurement. All subjects will receive a minimal behavioral platform for medical management (MM), that maximizes medication adherence in AUD treatment (44). We have well developed methods for subject recruitment, screening, and data management. This study will be conducted at our VCU Institute for Drug and Alcohol Studies site in Richmond or in the VCU Health Motivate clinic. Subjects will be pre-screened by telephone and if suitable, will be screened further in person. Study physicians will evaluate all subjects with medical/psychiatric history and physical exam. Subjects will participate in twelve total study visits and will be paid a total of $800 in cash, by check or clincard.

Inclusion Criteria: a) Men and women ages 21-70 with DSM-5 AUD; b) regular heavy drinkers as defined by averaging ≥ 2 heavy drinking days per week over the 60 days baseline

pre-treatment TLFB, and recognize a need to completely stop drinking; c) willingness to provide written, informed consent to participate in the study; d) Individuals with LFTs that are no more than 2-3 times above the normal levels and with a Child-Pugh score of no greater than 5 will be included and e) 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.

Exclusion criteria: a) a current, clinically significant physical disease [i.e., neurologic, renal, pulmonary, cardiovascular, hepatic] 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 exclusionary disorders include; b) history of renal compromise or current renal disease (as evidenced by serum creatinine above our laboratory's reference limit of 1.7 mg/dL; c) history of seizure disorder; d) use of any of a number of medications that might prominently influence drinking patterns or cause risk of harm or injury (e.g., other anticonvulsants, medications to treat AUD, opioid pain medication), currently taking CNS depressants (e.g. benzodiazepines, barbiturates, sedating antihistamines; e) schizophrenia, bipolar disorder, current major depressive episode, or substantial suicide or violence risk on the basis of history or psychiatric examination; f) currently dependent on, stimulants, opioids or sedatives; g) subjects with any substantial alcohol withdrawal will be required to be detoxified by regular clinical services prior to study entry; g) are currently taking any medication that is a moderate to strong CYP3A4 inhibitor or inducer if participants are required to initiate these medications by an outside provider during the course of this study, they will be tapered off the study regimen and we will have them terminate early) h) are taking phenytoin or warfarin

Study Procedures:

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. 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 Practitioner (NP) will obtain a medical and psychiatric history, and perform a physical exam. Drinking data for the 60 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), 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. This visit may be split into two clinic visits.

6.E.2. Visit 2 (Baseline Visit): After the screening visit, eligible patients will undergo the baseline visit prior to randomization. They will complete a packet of questionnaires. The subject begins a 3-week titration phase, during which the perampanel dosage will be titrated up as indicated below in Table 1, to a maximum of 8mg/day and disulfiram will be dosed as indicated in Table 1. Subjects will receive compensation for all visits, including follow-up visits (see Table

3). Compensation will not be prorated. We will provide taxi rides to assist with return transportation from the clinic, as long as it is within bus line limits or a 20mile radius. Staff will work with participants to determine individual needs.

TABLE 1: Medication Titration Schedule

Week	*Perampanel dose*	*+/-Disulfiram dose*
1	**2 mg daily**	**62.5 mg daily**
2	**4 mg daily**	**125 mg daily**
3	**6 mg daily**	**187.5 mg daily**
4-8	**8 mg daily**	**250 mg daily**

6.E.4. Visits 2b-10 (Treatment and End-of-Treatment Visits): Patients will first receive counseling and study medication during a treatment session (visit 2b) scheduled on the same day as the baseline assessment. Patients will be given study medications consisting of Perampanel or perampanel/disulfiram and titrated up to a maximum of 8 mg/day of perampanel (see Table 1). Participants will be instructed to refrigerate study medication. We will use blocked stratified randomization with use of antidepressants/psychotropic (yes/no) and sex as the stratification variables. Block sizes of 4 in each stratum to achieve treatment balance throughout the randomization process. During the 8-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 weekly for visits until the end of the study. (Note: a research staff member will call the patient in the middle of each week to check on their wellbeing and safety. 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. Furthermore, the call will be used to assess for any suicidal, homicidal, or violent ideation, or any other untoward effects. Subject medication adherence will be monitored using a video application, downloaded to the participant's phone or tablet. A phone or tablet will be provided to participants who do not have a personal a phone or tablet. Participants will be instructed to open the app and video themselves taking two study medications, then sending the video to a secure cloud based server. The PI or Clinical Research NP will have access to view the video and confirm that medication was taken.

At each visit, the patient's breath alcohol level (BAL), weight, and vital signs will be measured. A BAL of less than .08 is required for each visit, and At screening, a BAL of less than or equal to .02 is needed for the consent process. 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) 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 8 sessions), the nurse will deliver the MM intervention. 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. At that last visit (visit 10) the subjects will be instructed to taper the medication at a rate of 2 mg every 4 days.

6.E.6. Visits 11 and 12 (Follow-up): A follow-up visit will occur weekly for two weeks after the patient completes the 8 weeks of the study medication. These visits will last approximately 1 hour and the patient will be asked to complete the same surveys they had completed during the weekly visits and will be assessed as to how they are doing with the taper of the medication.

6.F. Study Treatments: Throughout the study, we will maintain open-label conditions regarding medication condition to optimize safety. 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 perampanel to be used in the present study is 8 mg/day. We will use a three-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 or stopped completely if necessary. 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. Perampanel and Disulfiram will be purchased commercially and dispensed by the VCU research pharmacy.

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 (44). 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 or violent thoughts) will be withdrawn from treatment and referred for appropriate clinical care.

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 (45).

6.G.1. Laboratory/Medical Assessments: These assessments serve to: 1) screen patients for medical exclusion criteria, 2) assess potential adverse effects of perampanel, 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. Pregnancy testing and a CBC, CMP with LFTS, bilirubin will also be repeated at the midpoint which is planned to be week 4 but may be adjusted per patient visit needs. Subjects with elevated LFTs (from baseline) will be immediately withdrawn from medication and closely monitored until a return to normal levels. 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 4) and endpoint (week 8), GGTP will be repeated to corroborate self-reported alcohol consumption. Endpoint labs will also include CBC, CMP with LFTs, bilirubin.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), and Ethyl Sulfate (EtS) as biomarkers to verify subjective claims of drinking during the study.

6.G.2. Psychological/Behavioral Assessments: 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**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**+1**	**+2**
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**	2	3	4	5	6	7	8	+1	+2
AUQ		x	x	x	x	x	x	x	x	x	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
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		
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		
AADUD	x									x		
AEQ		x				x				x		
BIS		x										
BART		x										
CGI-I						x				x		
CGI-S		x										

PSS		x				x				x		
Q-LES-Q		x								x		
SCID Section E										x		
SCID-II (antisocial)	x											
SIP		x								x		
SLEI		x				x				x		
SRE		x								x		
Early Termination Form										x		
Med-Q										x		
Laboratory/Medical												
Study Week	SC	BL	1	2	3	4	5	6	7	8	+1	+2
Screening/Monitoring Labs	x			x		x		x		x		
DNA	x											
ETG/EtS (urine)	x	x	x	x	x	x	x	x	x	x		
Urine/blood pregnancy test	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 4 is the study midpoint; (2) TLFB data will be collected at each visit to cover the period since the last visit (baseline will be 60 days prior to randomization); (4) **Abbreviations:** SC: screening; BL: baseline; all other abbreviations can be found under the assessments sections of the project description] (5) Monitoring Labs will include a CBC and CMP 12+8AC

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 (46). We may opt to use an online version for ease clarity.

***d. Family history of alcohol dependence*:** The Family History Assessment Module (47) 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) (43) will be used to estimate past 60-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 (48, 49). 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), (50).

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 (51), 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)(52) (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;(53, 54) 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;(55) 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) (56) 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 (57, 58) will be administered at each visit. 2) The State-Trait Anxiety Inventory will be used to measure anxiety symptoms at each visit (59). 3) The Columbia Suicide Severity Rating Scale, C-SSRS (60) 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) 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 (61).

f. *Behavioral assessments*: Impulsivity will be assessed through the Balloon Analogue Risk Task (BART) and Barrett Impulsivity Scale (BIS).

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 (62), a widely used measure of adverse events. A standardized approach was developed for use in alcohol treatment trials (63).

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.

TABLE 3: Subject visit and payment overview:

Visit title	VISIT #	Weeks of completed medication	Payment ($)
Screening	1		50
Baseline	2	0	75
Weekly treatment visit	3	1	75
Weekly treatment visit	4	2	75
Weekly treatment visit	5	3	75
Weekly treatment visit (midpoint)	6	4	75
Weekly treatment visit	7	5	75
Weekly treatment visit	8	6	75
Weekly treatment visit	9	7	75
Weekly treatment visit (Endpoint)	10	8	100
Medication taper visit 1 (post treatment)	11	n/a	25
Medication taper visit 2 (post treatment)	12	n/a	25
Total	**12**		**800**

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.

D.3. Data Analysis/Power/Sample Size:

The 20 perampanel-treated subjects will be compared to 20 age and sex matched placebo-treated subjects (with stated goals of abstinence) from the databases of our completed and ongoing clinical trials. This quasi-experimental design will allow us to complete an informative and reasonably valid pilot study with substantially less cost and time. We will use ANOVA to compare the subjects between the two main groups (both perampanel vs placebo) for the **percent abstinent days** (primary outcome) during the eight-week study period. We will also compare the three groups directly (perampanel vs disulfiram/perampanel vs placebo). We will

explore several secondary outomes such as perampanel effects on craving, heavy drinking days per week, etc. using longitudinal mixed models. **Power analysis**: No studies have examined the clinical response to perampanel in AUD, but we should have power = .80 to detect effect sizes = .45 or greater. The secondary outcome analyses with mixed models will have greater power.

Personalized Medicine Analysis: In this aim we plan to elucidate metabolic and genetic variable important for perampanel efficacy in the treatment of AUD. For the drug Acamposate, which is thought to inhibit glutamate in the brain, elevated baseline levels of glutamate in serum are associated with positive response to treatment for AUD. Since Perampanel is a glutamate receptor antagonist, it is logical that elevated serum glutamate levels may also be a biomarker for Perampanel effectiveness against AUD.

Measurement of glutamate levels in the serum: To determine if serum glutamate levels effect the patient's response to perampanel treatment for AUD serum will be drawn at multiple time-points during the clinical trial described in Aim 1: baseline levels (before treatment), after each treatment regimen (perampanel).

In addition to glutamate as a biomarker this aim will also examine the role of genetic polymorphisms in response to Perampanel. DNA samples will be genotyped on the Illumina PsychChip GWAS array. We will focus on 127 SNPs in 13 genes from the NMDA-dependent AMPA receptor trafficking cascade as identified by Karpyak and colleagues as predictive of AUD in our analysis of perampanel's effects on alcohol response. We will use the genotype at these SNPs to construct a genetic risk prediction score (GRPS) variable for each subject, which allows us to easily include a variable to be compared between-subjects, and eliminates issues with multiple testing. The GRPS represents the degree of genetic loading with AUD-risk variants across the AMPA-R related gene set.

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