LACOSAMIDE EFFECTS ON ALCOHOL SELF ADMINISTRATION AND CRAVING IN HEAVY DRINKERS

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Sponsor: NIAAA/NIH
Principal Investigator: Eric G. Devine, Ph.D.
Phone: 617-638-7888
E-mail: eric.devine@bmc.org

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TABLE OF CONTENTS

1 List of Abbreviations

Abbreviation	Abbreviation definition
Alcohol Use Disorder	AUD

2 Protocol Summary

Title:	Lacosamide effects on alcohol self administration and craving in heavy drinkers.
Population:	The present study will involve 112 men and women aged 21 to 55 who exceed safe levels of drinking. Women and minorities who meet the study criteria will be eligible to participate. No vulnerable populations are being targeted for inclusion in this study
Intervention:	Eligible subjects will be titrated to a target dose of 300mg of lacosamide (or a matched placebo) over a 7-day period. A riboflavin tracer will be added to each capsule to serve as an objective measure of medication adherence. Subjects will receive a single 150 mg dose of lacosamide on day 8. Subjects will take study medication by mouth. Subjects will receive alcohol in the laboratory on day 8 in an alcohol craving challenge. Subjects will be presented with four drinks, each mixed to raise their BAL 0.015g/dl. They will be told that they can either consume the desired number of drinks over the following 60 minutes or they will receive the equivalent in a cash reward. This procedure will be repeated with an additional 4 drinks after 60 minutes has elapsed. Subjects will serve as their own controls. The intervention will be repeated with a placebo/lacosamide after a washout period. The order of lacosamide and placebo dosing will be randomized.
Objectives:	The specific objective of this study is to determine whether lacosamide, a novel anticonvulsant that is FDA-approved for treating partial seizures, has effects on alcohol craving and consumption. This medication is a promising candidate that has unique actions on voltage-gated sodium channels and may have inhibitory effects on collapsin response mediator protein-2 (CRMP-2). Testing the effects of lacosamide on drinking is a compelling opportunity that is consistent with the mission of NIAAA to evaluate the efficacy of re-purposed compounds with novel mechanisms that have the potential to treat AUD. If successful, this study could lead to a phase II randomized controlled trial to test lacosamide as a treatment for AUD. The specific goal of this study is to evaluate the effects of lacosamide on drinking and craving among heavy drinkers in a human laboratory using an alcohol self-administration

	paradigm.
Design/Methodology:	This is a double-blind, randomized, placebo-controlled, crossover design trial that will test the effect of lacosamide on alcohol self-administration and craving following a priming dose of alcohol. An established human laboratory self-administration procedure will be followed. Each subject will complete 5 clinic visits over a period of up to 44 days of participation. Study participation is comprised of a baseline assessment, randomization visit, alcohol self administration Trial 1, an assessment visit to verify continued eligibility and dispense medication, and a second alcohol self-administration Trial. The volume of alcohol consumed during alcohol challenge trials 1 and 2 will be used to test the effect of lacosamide on alcohol consumption. Craving measures (AUQ and VAS) collected during the self-administration trials will be used to test the effect of lacosamide on alcohol craving.
Total Study Duration:	The entire study will take 24 months to complete.
Subject Participation Duration:	Each subject's length of participation will be up to 44 days.

3 Background/Rationale & Purpose

3.1 Background Information

Current models of care for treating Alcohol Use Disorder (AUD) include both behavioral therapies and pharmacotherapy[1]. Although pharmacotherapy for AUD in the US has been available since 1948 when disulfiram was approved, options for treatment are limited as there are only four medications which have been approved by the FDA for treating AUD. Disulfiram, naltrexone, acamprosate, and long-acting naltrexone have all shown promise as agents to treat AUD[2] but no single medication has proven to be effective across the heterogeneous groups of people with AUD[3]. Movement towards models of personalized care and pharmacogenetic treatment matching[4-5] hold some promise for improving AUD treatment outcomes, but the limited number of unique mechanisms of action of the currently approved drugs presents a challenge to implementing this model of care. Unfortunately, few novel compounds to treat AUD progress to phase II trials, and developing novel compounds is both costly and time-consuming[6]. One pathway of drug development efforts has been focused on re-purposing FDA approved medications that have promising mechanistic effects[7] and some success has been achieved in using this strategy with anticonvulsants[8]. Identification of additional drugs with unique mechanisms of action that are found to reduce alcohol consumption could expand the treatment options and further the goal of personalized care for AUD. The overarching goal of our research is to identify agents with unique mechanisms that hold promise for treating AUD. The specific objective of this study is to determine whether lacosamide, a novel anticonvulsant that is FDA-approved for treating partial seizures, has effects on alcohol craving and

consumption.

Alcohol Use Disorder as a national health problem

More than 16 million adults suffer from Alcohol Use Disorder (AUD) in the United States[8.] The economic burden of this is estimated to be 249 billion dollars and approximately 88,000 Americans die from alcohol-related causes each year[9]. Untreated AUD is associated with an increased risk of accidents, injuries, suicide, and worsening of other health comorbidities[10] and it is the fourth most preventable cause of death in the US[9]. Treating addiction more effectively has become a priority of national importance and the Surgeon General has urged researchers to undertake testing of new treatments to combat addiction[11]. The present study is intended to answer the call for accelerating drug development for AUD by exploring the potential to re-purpose an existing drug as a treatment for AUD[6-7].

Rationale for developing lacosamide as an agent to treat AUD

Lacosamide is a D-serine analogue that is approved for use as a therapeutic agent for treatment of partial seizures[12]. In contrast to other anticonvulsant agents, this drug decreases seizure activity, in part, by enhancing slow sodium channel inactivation[13-14]. The administration of lacosamide to either mice (C57Bl/6J) or rats (Long Evans) has been shown to significantly reduce their intake of alcohol in a model of 'excessive' drinking[15]. This finding is of interest because the predominance of evidence suggests that in addition to its action on sodium channels, this anticonvulsant binds to and inhibits the activity of collapsin response mediator protein-2 (CRMP-2)[16-18]. Alcohol consumption in mice that had knockdown of CRMP-2 within the nucleus accumbens (a mesolimbic structure that regulates alcohol consumption and seeking behaviors) was decreased from levels seen in control animals[15]. This finding implicates CRMP-2 as having a role in the regulation of alcohol consumption.

Based on the finding that lacosamide decreases alcohol consumption in rodents, we plan to test our hypothesis that this drug will have similar effects on the self-administration of alcohol by human subjects. Confirmation of this hypothesis would be of particular significance because CRMP-2 is a downstream target of the mammalian target of rapamycin complex 1 (mTORC1)[15, 19]. Several studies implicate mTORC1 in the development of the neuroadaptations that are involved in the seeking and consumption of a wide range of abused substances including alcohol[26]. Administration of the mTORC1 antagonist rapamycin into the nucleus accumbens has been shown to decrease alcohol consumption and seeking behavior in rats[21]. In addition, systemic and intra-amygdalar micro-infusion of this drug appears to disrupt memories of alcohol-related cues and thereby suppresses behavior in rodent models of drinking and relapse[22]. These results suggest that rapamycin or other drugs with similar mechanistic effects may have efficacy as medications for the treatment of AUD through a mechanism that is not targeted by any medications currently used to treat AUD.

Rapamycin (sirolimus) is approved for use as an immunosuppressant agent, but it can produce toxic effects including myelosuppression and leukoencephalopathy which would constitute an unacceptable risk in an AUD population. Testing of medications that act on targets downstream of mTORC1 that are less toxic than rapamycin may prove to be a useful approach in the development of drugs for the treatment of AUD through this novel mechanism. The findings of Liu and colleagues suggest that CRMP-2 may be an important downstream mTORC1 target for medications that will produce reductions in alcohol consumption because this protein may play a role in the neuroplastic changes associated with the development of excessive drinking. These changes may be related to alcohol-induced changes in the characteristics of neuronal

dendritic spines and related alterations in the activity of select neurotransmitter systems[23-25]. Liu and his co-investigators reported that the mTORC1 antagonist rapamycin blocks alcohol mediated increases in CRMP-2 polysomal messenger RNA within the nucleus accumbens. Indeed, CRMP-2 protein levels within the nucleus accumbens of the rat have been found to be elevated after episodes of alcohol consumption. CRMP-2 stabilizes microtubules within dendrites and may promote neurite outgrowth. Interestingly, lacosamide has been shown to block CRMP-2-induced neurite complexity in cultured brain cortical cells, suggesting a possible mechanism through which this medication may block alcohol-induced changes in neuroplasticity[26].

Lacosamide fits the description as a medication that modulates the activity of a downstream target protein of mTORC1 that appears to regulate alcohol consumption in rodent models. In contrast to rapamycin, this drug has been found in clinical trials to be well tolerated, producing dose related adverse effects including dizziness, nausea, and diplopia that were in the mild to moderate range[27] and that are common adverse effects produced by almost all anticonvulsant drugs. When used as monotherapy, a small percentage of patients had to discontinue lacosamide therapy because of the occurrence of rash, dizziness, headache, somnolence and elevations in liver function tests (i.e.γ-glutamyl transferase and aspartate aminotransferase)[28]. There are two post-marketing reports of heart block occurring in patients who were treated with a combination of lacosamide and the beta-adrenergic receptor antagonist metoprolol[29]. Major concerns with the occurrence of severe skin rash, hepatoxicity, suppression of white blood cell production, or weight gain that are associated with the use of certain other anticonvulsant medications have not been reported to be a problem in patients treated with lacosamide.

Treatment with the broad spectrum anticonvulsants topiramate and zonisamide, which are reported to reduce alcohol consumption in AUD subjects, is associated with the occurrence of deficits in cognitive functioning including impairment of verbal fluency and working memory[30]. These adverse cognitive effects may limit their acceptability for the treatment of AUD for many individuals. The administration of lacosamide as compared to topiramate, when these drugs are used as adjunctive agents, may be less likely to adversely affect cognitive function in epilepsy patients[31]. Lacosamide also appears to be less likely than the anticonvulsant carbamazepine to impair performance on a wide range of neuropsychological tests[32]. In a study of the effects of lacosamide in patients with partial seizures, no significant differences in COWAT scores were found between weeks 1 and 28 of treatment with this drug when administered in doses ranging between 100 to 400 mg per day[33]. Lacosamide was found to produce a significant, but modest, reduction in WAIS-III Digit Span scores (a test of working memory) collected for these patients. We believe that lacosamide is a promising agent for drug development given the novel mechanism of action, positive findings in animal models, and an acceptable safety profile.

In this study, the effects of lacosamide on cravings will also be assessed. This is important because cravings that follow alcohol consumption may be important factors in motivating drinking[34-36]. The effects of anticonvulsants on these factors in the context of alcohol challenge and self-administration studies have not been extensively examined. In an alcohol self-administration study testing zonisamide, we found that reductions in craving occurred in association with reduced alcohol self-administration[37]. These results are similar to those showing that naltrexone administration leads to significant corresponding reductions in alcohol self-administration and craving scores[38]. Understanding the effect of lacosamide on craving and stimulant effects of alcohol may inform our understanding of how lacosamide impacts drinking.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

3.2 Rationale and Purpose

This study holds significant innovation as there is mounting evidence that medications that act on targets downstream of mTORC1 have the potential to decrease craving and consumption, but no medications have been developed to date to take advantage of this novel mechanistic approach. Two medications which impact the mTORC1 pathway, lacosamide and rapamycin, have been tested in rodent models and both medications have been shown to reduce alcohol consumption[15,21]. Rapamycin is not a promising candidate for drug development due to the potential for serious adverse effects, but lacosamide is promising given the findings from animal models, the tolerable safety profile, and the low incidence of cognitive adverse effects relative to other anticonvulsants used to treat AUD. To date, there have been no controlled studies testing lacosamide in human drinkers that either have been published or registered with Clinicaltrials.gov. The study answers the call for accelerating the development of medications for AUD by testing a commercially-available and well-tolerated agent at a fraction of the cost of developing novel therapies. If successful, this study could lead to a phase II randomized controlled trial to test lacosamide as a treatment for AUD.

4 Objectives

4.1 Study Objectives

The specific objective of this study is to determine whether lacosamide has effects on alcohol craving and consumption. This medication is a promising candidate that has unique actions on voltage-gated sodium channels and may have inhibitory effects on collapsin response mediator protein-2 (CRMP-2). Testing the effects of lacosamide on drinking is a compelling opportunity that is consistent with the mission of NIAAA to evaluate the efficacy of re-purposed compounds with novel mechanisms that have the potential to treat AUD.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

The primary outcomes are alcohol consumption and cravings during the alcohol self-administration trials. Drinking volume during the alcohol self-administration will be measured to evaluate the effects of lacosamide vs. placebo on the rate of alcohol consumption after a priming drink. Alcohol craving will be measured using the Visual Analog Scale (VAS) and the Alcohol Urge Questionnaire (AUQ)[39] during the lacosamide self-administration trial. These self-report measures of craving will be used to evaluate the effect of lacosamide on craving vs. placebo.

4.2.2 Secondary Outcome Measures

Secondary outcome measures for this study include the effect of lacosamide on 1) cognitive

function, and 2) alcohol use and craving during the titration period**.** The Controlled Word Association (COWAT)[40] and the Wechsler Adult Intelligence Scale (WAIS-5)[41] Spatial and Digit Span tests will be used to assess the effects of lacosamide administration on cognitive function. The Obsessive-Compulsive Drinking Scale (OCDS)[42], and the alcohol VAS will be used to assess the effects of lacosamide on craving during the medication titration period.

5 Study Design

This is a double-blind, randomized, placebo-controlled, crossover design trial that will test the effect of lacosamide on alcohol self-administration and craving following a priming dose of alcohol. An established human laboratory self-administration procedure will be followed[38]. The O'Malley self-administration procedure entails the administration of a priming drink followed by the presentation of four drinks on a tray which subjects may drink, or receive compensation for the drinks not consumed. After one hour the first tray of drinks is removed and subjects are then given the opportunity to consume a second tray of drinks. Confirmation of the validity of this approach as a method for screening for medications to treat AUD include the finding that pre-treatment with naltrexone, which is an approved medication for treating AUD, significantly reduced alcohol consumption when the O'Malley self-administration procedure was used[45]. Using this procedure, our group has found that the anticonvulsant zonisamide reduces alcohol consumption in non-treatment seeking social drinkers[43]. We later confirmed that the administration of zonisamide decreases alcohol consumption in subjects with AUD in a double-blind randomized clinical trial[25] as have other investigators[43]. Testing lacosamide using O'Malley's self-administration procedure is the next logical step in drug development following positive findings that lacosamide reduces drinking in animal models. The human laboratory-based alcohol self-administration procedure is a cost effective and time-efficient method for testing novel drug candidates for AUD treatment[6].

Subjects: Heavy-drinking subjects will be enrolled to increase the potential generalizability of these findings to a clinical AUD population. Subjects will be recruited through radio advertisements, newspaper advertisements, internet advertisements, study flyers, internet postings, and an established subject registry at Boston Medical Center. Interested subjects will be screened by telephone to determine initial eligibility prior to the baseline assessment.

6 Potential Risks and Benefits

6.1 Risks

Risks of study medication (see product insert)

To minimize the risk of adverse health events we will instruct subjects to contact study staff with any questions or concerns about changes in health effects after initiating study medication/placebo. Trained medical staff will evaluate any reported adverse effects and make a clinical determination about management through dosing methods (e.g., taking before bedtime or with food), dose discontinuation, and/or referral for medical care. Subjects will be given a wallet card that includes a phone number with 24/7 coverage for medical emergencies. As an added

safety precaution, subjects will be contacted mid-week of the titration period for an adverse effect assessment.

Adverse effects

Treatment emergent adverse events (TEAs) in studies of the effects of lacosamide are shown in the three tables below. Of most relevance to this protocol are findings from the TEAs in healthy subjects shown in Table 1. The least tolerated dose reported for healthy subjects was found in a study that subjects that received 400 mg per day of lacosamide for 6 days without a period of drug titration[44]. Roughly 8% of subjects in this study reported feeling drunk at this dose.

Table 1. Common TEAs for healthy subjects obtained in 3 studies

TEA	Healthy (n=20)[45]	Healthy (n=50)[46]	Healthy (n=56)[44]	Healthy (n=54)[44]
	300mg	300 mg	400 mg	Placebo
	6 Weeks	21 Days	6 days	6 days
	3 Week Titration	3 Week Titration	No Titration	No Titration
Dizziness	2%	7.4%	10.0%	6.5%
Somnolence	4.0%	11.1%	Not Reported	Not reported
Headache	10.0%	11.1%	16.7%	14.5%
Nausea	4.0%	Not reported	8.3%	1.6%

Data from seizure patients who received lacosamide as monotherapy is presented in Table 2[47]. At the 300 mg dose these patients showed a greater incidence of dizziness, nausea, and headache than did healthy subjects treated with this dose. Data from the monotherapy study also includes findings from when subjects were also receiving other anticonvulsant medications.

Table 2. Findings for lacosamide monotherapy studies.

TEA	Monotherapy[47]	Monotherapy	Monotherapy Newly Diagnosed Subjects[48]
	300mg	400 mg	200-400 mg/day
	N=106	N=319	N=444
Dizziness	17.9	26.0	12%
Somnolence	14.2	9.1	5%
Headache	17.9	13.2	14%
Nausea	12.3	13.8	6%
Blurred Vision	5.7	6	Not reported

Table 3 includes data from seizure patients treated with lacosamide in combination with other anticonvulsant drugs during the titration phase for lacosamide.

Table 3. Pooled percent common TEAs for focal seizure patients treated with lacosamide as an adjunctive medication obtained for the titration phase of 3 RCT's.[49]

TEA	200 mg (n=270)	400 mg (n=471)	Placebo (n=364)
Dizziness	10.4	24.6	6.6
Fatigue	6.7	6.8	5.2
Ataxia	2.2	5.9	1.4
Balance Disorder	0.7	3.6	0.0
Nausea	5.6	8.5	3.6
Blurred Vision	1.9	6.2	1.6
Diplopla	4.4	8.3	1.1

Risks of Dizziness. Ataxia, Somnolence, and Incoordination

Data presented in the tables shown above suggest that there may an increased risk of dizziness,ataxia, somnolence, and incoordination associated with the administration of lacosamide to healthy subjects. Consequently, subjects in this study will be counseled that the administration of lacosamide may produce dizziness, double vision, somnolence, and problems with balance and coordination. They be advised to avoid driving, operating complex machinery, or engaging in other hazardous activities until they have become familiar with the effects of lacosamide.

Physical discomforts:

The drawing of blood may cause pain, bruising, lightheadedness, and on rare occasions, infection. Subjects may briefly feel the prick of the needle when it is inserted. Subjects may feel dizzy or faint when blood is drawn. Trained phlebotomists will be used to minimize these risks.

ECGs may cause discomfort and/or irritation of the skin (redness and itching) from the adhesive electrodes. Hair on your chest may need to be removed in order to obtain the best electrical contact between the adhesive electrodes and subjects' skin. Trained staff will be used to minimize these risks.

Cardiac Risks

A dose dependent prolongation of the PR interval has been observed in both patients and healthy subjects who have received lacosamide. Asymptomatic atrioventricular (AV) block has been observed in clinical trials in 0.4% of patients being treated for seizures and 0.5% of patients being treated for diabetic neuropathy. Cases of second degree and complete atrioventricular block have been seen in both seizure and pain patients. In two postmarketing reports, third degree AV block was observed in patients who had a significant cardiac history and were being treated the beta blocking drug metoprolol and the calcium channel blocker amlodipine when receiving infusions of lacosamide at above the recommended doses for this drug. Bradycardia also has been observed in patients who have received intravenous infusions of lacosamide.

No cases of atrial fibrillation or flutter were observed in the short-term investigational trials of lacosamide seizure patients. Cases of atrial fibrillation and atrial flutter, however, have been detected in both open label epilepsy trials and in postmarketing experience. In patients who had diabetic neuropathy, 0.5% of patients had episodes of atrial fibrillation or atrial flutter while no episodes of these disorders occurred in placebo-treated patients.

It is recommended that lacosamide be used with caution in patients with previously identified conduction problems including marked first-degree AV block, second-degree or higher AV

block and sick sinus syndrome without pacemaker), sodium channelopathies, a history of myocardial infarction or congestive heart failure. Its use should be avoided in individuals who are receiving other medications that may prolong the PR interval.

To minimize the risk of cardiac adverse events, the published caution guidelines will be used to exclude patients from entering this study. All study candidates will receive an ECG to detect disturbances in cardiac function that may place them at risk for a cardiac conduction problem if they were to receive lacosamide. Patients will be excluded if either the results of the ECG recording or their medical history indicates that they would be at risk of developing cardiac problems from lacosamide use. Study candidates will also be excluded from study entry if they are taking any medication that may block cardiac conduction. This will include the use of any antiarrhymic agents including beta and calcium channels blockers and digoxin.

Psychiatric risks

In clinical trials of the effects of antiepileptic drugs (AED), the incidence of suicidal behavior or ideation was 0.43% in AED-treated-subjects versus 0.24% for placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 treated patients. These trials included 27,863 patients being with AED and 16,029 patients to who placebo was administered. There were four suicides in drug-treated patients in these trials and none in the placebo-treated patients. Because of these finding treatment with any anticonvulsant medication including lacosamide must be considered to produce to an increased risk of suicidal thoughts and behaviors.

To minimize the risk of worsening suicidal thoughts and behaviors we will screen for suicidality using the Columbia-Suicide Severity Rating Scale and the MINI Neuropsychiatric Interview. Subjects with a MINI suicidality score greater than 8 (low risk) will be excluded. Subjects who report any active suicidal thoughts or behavior as measured the C-SSRS will be excluded from participation. In addition to excluding active suicidality, the MINI will be used to rule out subjects who have psychiatric conditions that may increase the risk of the occurrence of suicidal thoughts or behavior (e.g., major depression, bipolar disorder). Assessment and scoring of suicide rating scales will be conducted in real-time while the subject is present. Suicidality will be assessed by trained clinical staff including study MDs, a psychologist, a nurse, and a mental health counselor. If subjects are found to be at risk for self harm, study staff will work with the subject to develop a safety plan that could include escorting the subject to the BMC ED or calling BEST. To minimize the risk of abuse of lacosamide, subjects with lifetime substance use disorders will be excluded (with the exception of marijuana, caffeine, nicotine and alcohol). To date, there are no published reports of the abuse of lacosamide.

Risk to a developing fetus

The administration of lacosamide to pregnant rats has been found to produced developmental toxicity that included increased embryofetal and perinatal mortality, and growth deficits. following administration during pregnancy. Neurotoxicity has been seen in rats who received this drug during a period of postnatal development believe to correspond to the third trimester of human pregnancy.

To protect against the risk of potential developmental toxicity to a fetus, women will be excluded from study entry if they have a positive urine pregnancy test or if they are of childbearing age and are either not using appropriate methods of contraception or not practicing abstinence. Urine

pregnancy testing will also be completed at each study visit as a protection to the developing fetus. Subjects with positive pregnancy test results will be discontinued form participation

Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity

During the clinical development of lacosamide one case of symptomatic hepatitis and nephritis was observed among 4011 subjects exposed to this drug. This happened in a healthy volunteer, 10 days after the discontinuation of lacosamide. This case was deemed to be consistent with a delayed multi-organ hypersensitivity reaction. Other possible cases included two subjects who had a rash and elevated liver enzymes and one subject who had myocarditis and hepatitis of uncertain etiology. We ask that subjects contact a study physician immediately if they develop a rash, fever, become excessively tired, notice that their urine turns brown, or notice your skin turning yellow.

Risk of Stevens Johnson Syndrome /Toxic Epidermal Necrolysis

Post-marketing data indicate the occurrence of cases of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis in patients being treated with lacosamide. This data does not allow for determination of a reliable estimate of frequency of occurrence these disorders being treated with lacosamide nor do they establish a causal relationship between appearance of these disorders and exposure to this anticonvulsant. Subjects will be asked to contact a study physician immediately if they develop a rash, fever, sore throat, mouth ulcers, or bruising while taking the study medication.

Risks of alcohol self-administration

Risk to recovery efforts

Treatment-seeking drinkers will be excluded from this study to minimize the risk that drinking in the laboratory could worsen outcomes for a subject trying to reduce or abstain from alcohol. All subjects will undergo a medical screening and we will exclude subjects who have a medical or mental condition for which alcohol exposure in this study would be contraindicated. All subjects will receive the NIAAA self-help guide *Rethinking Drinking* at the end of study participation.

Risk of overconsumption

To minimize the risk of subjects reaching a level of intoxication that is uncomfortable to them, we will remind subjects that they may discontinue study participation at any time. Subjects will be asked to drink to a target BAL (.03 g/dl) that is customary for them given the minimum drinking criteria. The alcohol self-administration paradigm that we have chosen does not include any coercion, inducements, or pressure to consume more alcohol than subjects feel comfortable consuming. There are no experimental manipulations that would increase drinking (e.g., heavy drinking confederate, anxiety manipulation). In fact, in this study design there are inducements for subjects to not drink beyond the initial priming dose. Subjects will receive monetary incentives for each drink that they do not consume. Access to medical backup services will be maintained throughout each alcohol challenge session. Subjects will be monitored during the course of the study, both through direct assessment with study staff and by observation through a video camera. Medical staff will evaluate subjects and may make a determination to halt study

participation if the subject becomes too behaviorally impaired or if there are emergent safety issues. Subjects who have a BAL greater than .04 g/dl or who appear to be too behaviorally impaired to leave our research center will be asked to remain in the clinic until their intoxication is reduced to a level that it is safe to discharge them from the research laboratory. BAL readings will be taken twice to confirm BAL is not greater than .04 g/dl prior to release. Subjects will not be released within 60 minutes of their last drink consumed to ensure that peak BAC has been reached prior to discharge. During the descending BAL period, subjects will have access to a comfortable space with entertainment (streaming media), snacks, non-alcoholic beverages, and a nearby bathroom.

Risk of loss of confidentiality

There is some risk that health information collected as part of this study could be seen by unauthorized individuals. Every effort will be made to minimize this risk and protect subject confidentiality. Electronic data will be housed in the REDCap data management system. REDCap is protected via Secure Sockets Layer (SSL) encryption that provides access restriction options. Exported data from REDCap will be stored on a secure password-protected server behind the BMC firewall. Source and CRF binders will be stored in a double-locked area that is accessible to only study staff. Subjects will be assigned a study identification number and this will be used to code any forms that do not require the subject's direct identifiers (e.g., consent form, laboratory results, and contact information). A linking key that associates study ID with direct identifiers will be stored in a double-locked cabinet accessible only by study team members. Data will be stored on a password-protected computer accessible only to the study team. Video of subjects during the drinking session will be stored on an encrypted drive with password protection. Video files will be deleted at the end of the study. All study staff will receive appropriate training for the protection of human subjects (NIH Protecting Human Research Participants, CITI Training). A certificate of confidentiality will be sought to protect subjects from disclosure under court order or subpoena.

6.2 Potential Benefits

There is no potential direct benefit to participation in this study. This study presents a very strong potential for benefit to science. Drug development for treating AUD is costly and few pharmaceutical companies are testing novel compounds as agents to treat AUD. Re-purposing compounds with FDA approval for other indications is the most promising route for rapid and cost-effective development of medications to treat AUD. This study will bridge the gap in drug development by providing a test of lacosamide to see if it may be a candidate drug for treating AUD. If successful, this could lead to the expansion of pharmacotherapy options to treat AUD and a broadening of our understanding of the mechanistic approach to treating AUD.

6.3 Analysis of Risks in Relation to Benefits

Given that lacosamide has FDA approval for another indication and is well-tolerated in other populations, the risk of this medication to human subjects has been established through pre- and post-marketing data. With the protections we have in place for all the potential risks in this study, we believe the risks of this study are well minimized. The study holds significant promise for

informing new models of care given the novel mechanism of lacosamide. We believe the risk/benefit ratio is favorable.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following inclusion criteria:

1. 21-55 years of age
2. Can provide proof of age with state-issued or federal picture ID
3. Exceeds safe weekly drinking limits (≥14 drinks for women or ≥21 drinks for men per week)
4. Reports at least an average of one episode per week of binge drinking (>3 for women, >4 in the four weeks prior to baseline screening
5. Meets DSM-5 criteria for mild alcohol use disorder or greater severity.
6. Have a smartphone to complete some of the study assessments.

7.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Currently seeking treatment for alcohol problems
2. Clinical Institute Withdrawal Assessment at >10
3. DSM-5 diagnosis of current major depression, bipolar disorder, schizophrenia, bulimia/anorexia, dementia, or a substance use disorder other than alcohol, nicotine, marijuana or caffeine
4. If female, pregnant, nursing, or have plans to become pregnant
5. If female, does not agree to use an accepted form of birth control
6. Is currently using medications for which alcohol is a contraindication
7. Has a medical or mental health condition for which further alcohol exposure at the planned dose range would be contraindicated.
8. Current risk of suicidality (MINI suicidality score greater than 8 (low risk) or Yes to the ideation question #4 of the C-SSRS)
9. Has a history of myocardial infarction, congestive heart failure, has a risk for the development of heart block, or are taking medications that can decrease conduction through the atrial ventricular node.
11. Has previous exposure to lacosamide
12. Has received any form of counseling, self-help, pharmacotherapy, or other intervention to treat AUD in the past 90 days.
13. Is unwilling to suspend use of multivitamins that contain riboflavin during study participation
14. Has urine toxicology results positive for cocaine, opioids, amphetamines, buprenorphine, methadone, or methamphetamines
15. Liver function values AST or ALT are twice the normal limit
16. GFR <80 mL/min
17. Unable to comfortably abstain from nicotine for a period of 8 hours.

8 Study Intervention

Study Medication

Study medication will be purchased and packaged by the BMC Investigational Pharmacy Service. Lacosamide (100mg and 150mg tablets) will be over-encapsulated with 50mg of riboflavin which will serve as a tracer of medication compliance. Matching placebo will also be packaged using lactose and 50mg of riboflavin. Medication will be dispensed to each subject in two bottles: 1) 11 pills of Lacosamide (100mg) or placebo 2) 3 pills of lacosamide 150mg or placebo. Capsule size required will be determined by IPS with the goal of a minimum capsule size needed for over-encapsulation. If a subject reports losing (or destroying) study medication, a replacement prescription will be written by one of the study physicians and the BMC Investigational Pharmacy will dispense additional medication to replace the lost (or destroyed) medicine.

Dosing

Subjects will take a single 100mg capsule in the evening of randomization day. Subjects will take 100 mg of lacosamide (or placebo) twice per day from day 2 through day 6. On day 7 subjects will increase to 150mg twice daily. Based on the metabolism of this drug, we expect to be within range of 90% of steady state for a 300 mg daily lacosamide dose by day 8 when the alcohol challenge trial will occur which is consistent with the clinical dose range (300-400mg daily as monotherapy) of this drug when it is used for seizure disorders[55]. Subjects who are unable to tolerate the titration period will be discontinued from the study.

Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Self-Admin
AM		100mg	100mg	100mg	100mg	100mg	150mg	150mg
PM	100mg	100mg	100mg	100mg	100mg	100mg	150mg	

Medication Storage

Medication will be stored in the Investigational Pharmacy at room temperature (within the range of 59°F to 86°F) in a secured area until the time that medication is needed for study subjects. Stability and expiry will be monitored by IPS according to the labelling of the medication from the manufacturer.

Medication Labeling

The study number will be preprinted on each bottle label. The label will include the drug name (e.g., Lacosamide XXXmg or placebo"). The label will also have a randomization number, the number of tablets contained in the bottle, storage conditions, the 24/7 phone number of the clinical site, and places to record the subject number and the date dispensed. Additional fields may be added to this label to meet any regulatory requirements as determined by IPS.

Medication Blinding and Unblinding

Study medication and placebo capsules will be identically matched in appearance and the bottle labels will not reveal the drug identity. The Study PI and study physician(s) will make the decision to un-blind the identity of the study medication in the event that the study blind needs to

be broken to make medical decisions regarding subject treatment.

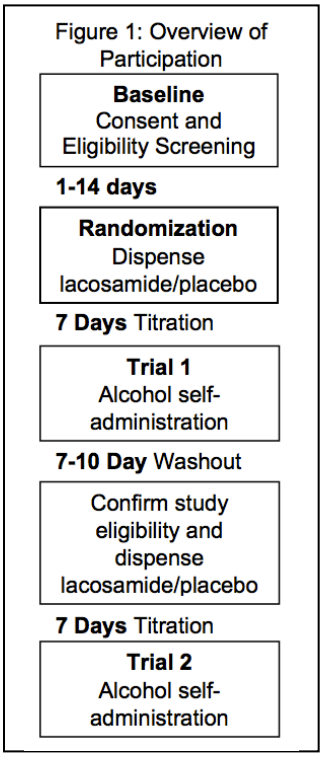
Medication accountability

The site principal investigator (PI) or designated study personnel will maintain a log of all study medication and record of dispensing of all medication to the subject. The site PI or his staff will count the tablets remaining at the end of the study and record the tablet count on the appropriate drug accountability form. Subject compliance with study medication will be assessed by comparing unused capsule count to dispensing logs and dosing records (number of tablets dispensed, number of tablets prescribed, versus the number returned). Subjects will also be asked to account for any missing tablets. If the bottle is not returned, the subject will be asked to report daily drug self-administration.

9 Study Procedures

Study Overview: Each subject will complete 5 clinic visits over a period of up to 44 days of participation. Study participation is comprised of a baseline assessment, randomization visit, alcohol self administration Trial 1, an assessment visit to verify continued eligibility and dispense medication, and a second alcohol self-administration Trial (see figure 1 for an overview of study participation).

Baseline assessment: Consenting subjects will undergo a general medical screen, physical examination, and electrocardiogram. Drinking will be assessed using the TLFB[50], alcohol withdrawal using the Clinical Institute Withdrawal Assessment[51], and suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS)[52]. Exclusionary mental health conditions will be assessed using the MINI Neuropsychiatric Interview for DSM-5[53]. Subjects will undergo laboratory testing that includes liver function, electrolytes, blood chemistries, urine analysis, urine toxicology and a urine pregnancy test for women of child bearing age.



Study randomization (medication visit #1): Qualified subjects will return to the clinic within 14 days for randomization to a crossover sequence of drug exposure. Subjects will be assigned to one of 2 groups , with one group receiving lacosamide prior to the first alcohol challenge trial and the other receiving lacosamide prior to the second alcohol challenge trial. Randomization of subjects will be accomplished using a stratified randomization procedure that will allow for between-group balance for drinking status (heavy vs. very heavy). Heavy drinking is defined as ≥ 21 and < 35 standard drinks per week for men, and ≥ 14 and < 28 standard drinks per week for women. Very heavy drinking is defined as ≥ 35 standard drinks per week for men, and ≥ 28 standard drinks per week for women. This stratified randomization will minimize the possibility that the order of treatment administration seems to influence outcomes when order effects are actually related to differences in severity of drinking between the two groups of subjects who are receiving the treatments in a different order. On the day of randomization, subjects will undergo an alcohol breath test, urine drug screening, assessment of concomitant medications, assessment of cravings, and drinking. Subjects who have purposefully abstained from drinking and achieved 7 days of abstinence prior

to the challenge will be excluded from participation for ethical reasons[55].

Titration period:
Randomized subjects will receive 8 days of study medication at the time of randomization. A riboflavin tracer (50mg) will be added to each capsule to serve as an objective measure of medication adherence on the day of the alcohol challenge[56]. Two bottles will be dispensed to each subject: 1) 11 pills of Lacosamide or placebo over-encapsulated with 50mg of riboflavin and 2) 3 Pills of lacosamide or placebo over-encapsulated with 50mg of riboflavin. Subjects will take 100 mg of lacosamide (or placebo) twice per day until day 7. On day 7 subjects will increase to 150mg twice daily. Based on the metabolism of this drug, we expect to be within range of 90% of steady state for a 300 mg daily lacosamide dose by day 8 when the alcohol challenge trial will occur which is consistent with the clinical dose range (300-400mg daily as monotherapy) of this drug when it is used for seizure disorders[57]. Subjects who are not able to achieve the target dose due to adverse effects will be discontinued from the study.

Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Self-Admin
AM		100mg	100mg	100mg	100mg	100mg	150mg	150mg
PM	100mg	100mg	100mg	100mg	100mg	100mg	150mg	

The seven-day period of medication titration will begin within a window of 6 days depending upon scheduling the alcohol challenge. Subjects may be randomized and instructed to start the medication up to 6 days later so that day 8 will conicide with the alcohol challenge appointment. Subjects will be given a brief phone reminder to start medication on Day 1. During the seven-day period of medication titration, subjects will be asked to answer a medication compliance question each day by smartphone using the REDCap data capture through a web-based portal[58]. In addition to assessing medication compliance, subjects will also be asked to rate their craving for alcohol each day using the alcohol VAS. Subjects will receive a $5 reimbursement on each day they complete the VAS and answer the medication compliance question using the REDcap web-based portal. Subjects will be contacted by telephone on day 3 of the medication titration period for an adverse event assessment.

Medication Visit #2
After the 7-10 day washout period subjects will return to the lab to receive study medication prior to the alcohol challenge #2. Subjects will complete the same tests and interviews completed during the randomization visit (See appendix A for schedule of events). Based on the assessments at medication visit #2, subjects be discontinued for the following reasons: pregnancy, recreational drug use, evidence of non-compliance with study medication, suicidal thoughts or behavior, and use of a new medication that would make participation unsafe. Subjects will receive an 8-day supply of study medication and will be scheduled for the alcohol challenge #2.

Alcohol Challenge Trials 1 & 2: Subjects will return to the laboratory on day 8 of titration for each medication trial to complete the alcohol challenge. For safety reasons, subjects will be asked to arrange transportation plans (no driving) prior each of the alcohol challenge trials.

There will be a 7-10 day washout period between alcohol challenge Trial 1 and medication visit 2. Based on the known half-life of lacosamide, all of the medication will be cleared within 7 days. The washout may extend to 10 days to accommodate the scheduling of Trial 2. Concomitant medications, urine drug screening, urine pregnancy testing, blood alcohol level will be assessed to determine eligibility to proceed with the challenge. Blood alcohol level must be 0.000 to continue with the study procedures. Urine collected for drug screening will be exposed to ultraviolet light as an objective test of medication compliance. If no fluorescence is observed in the urine sample the subject will be excluded from continuing with the challenge. Measures of drinking (TLFB), cravings, (OCDS and AUQ), and neurocognitive function (COWAT, WMSIII Spatial Span and Digit Span tests) will be collected to inform secondary outcomes. Subjects will be observed taking the morning dose of lacosamide (or placebo) on the day of the challenge (after compliance is confirmed via a urine screening). The peak plasma concentration of lacosamide should be reached approximately 60 minutes after administration. The alcohol self-administration session will begin no sooner than one hour after the administration of the observed 150mg morning dose. The alcohol self-administration will be conducted in the GCRU. The room will be a carpeted and furnished with a lounge chair, side table and television which allows access to popular streaming entertainment (e.g., Netflix, YouTube). A small unobtrusive camera is mounted in one corner to allow for monitoring without study staff being present in the room. The room has ready access to a bathroom. The alcohol self-administration is divided into four segments: 1) a 5-minute segment for the priming dose, 2) a 40-minute segment for observing alcohol's effects, 3) a 60-minute segment of alcohol self-administration (Block1) and, 4) a second 60-minute segment of alcohol self-administration (Block2) [see figure 2 for the alcohol self-administration Procedure].

Figure 2: Alcohol Self-Administration Procedure

Priming Dose	**Observation**	**Self-Administration Blocks 1 & 2**
5 minutes Drink mixed to achieve BAL= 0.03g/dl	40 minutes Craving and intoxication measured in 10-minute intervals	60 minutes each 4 drinks per block Each drink mixed to raise BAL 0.015 g/dl

Priming dose. Subjects will be given a priming drink designed to increase the subject's blood alcohol level (BAL) to 0.03g/dl, using the alcohol of their choice that is 24% Alcohol By Volume (ABV) or greater. The volume of alcohol will be calculated using an online tool developed by UW-Madison (http://dionysus.psych.wisc.edu/WebCMS/baccalc.htm) based on a formula described by Watson[59] The subjects will be asked to drink the priming drink over a period of 5 minutes. Part of the purpose of the priming drink is to normalize drinking in the laboratory.

Observation period. Subjects will be observed for 40 minutes following the priming dose of alcohol to allow for absorption of the alcohol.

Alcohol self administration Blocks 1 and 2. In each of the alcohol self-administration Blocks, subjects will be presented with four drinks, each mixed to raise their BAL 0.015g/dl. They will be told that they can either consume the desired number of drinks over the following 60 minutes or they will receive the equivalent dollar amount of the cost of each drink ($3.00) they did not consume before leaving the clinic. At the end of each 1 hour session the tray with the remaining drinks will be removed and the amount of alcohol remaining will be measured. Cravings will be

assessed using the AUQ and VAS every 30 min during the self-administration blocks. Based on the rate of alcohol metabolism over the time of the trial, we anticipate that subjects who consumed every drink could reach a BAC of .09 to .13 g/dl depending upon differences in alcohol metobolism. Safety assessments will be completed (intoxication, sedation, adverse effects) prior to subjects leaving the laboratory. Subjects will be required to have a plan for transportation home that does not involve driving. Subjects will not be released until their blood alcohol level is $\leq$ 0.04 g/dl and they are not behaviorally impaired. After the second alcohol self-administration trial has been completed subjects will receive a copy of the NIAAA publication *Rethinking Drinking*[60] and will be encouraged to review rethinking drinking materials online.

Subject compensation

Subjects will be compensated up to $418 for completion of all study activities. Subjects will receive a reimbursement of $40 for the screening visit, $20 for the randomization visit and $20 for the assessment visit prior to Trial 2. Subjects will receive $80 for each of the two alcohol challenge trials and a $40 completion bonus if they complete both challenges. Subjects will receive a $5 payment each on day during the two 7-day titration periods that they respond to the REDcap survey to rate their alcohol craving and report their medication compliance. Subjects will also receive a $10 completion bonus if they complete the craving scale and medication log on all seven days. Subjects may receive up to $48 dollars in payments for drinks not consumed during the two alcohol self-administration Trials.

In addition to this $418 of compensation, subject may also be reimbursed up to an additional $60 for distributing study recruitment materials to other people who may want to take part in this study. Distributing recruitment materials is completely optional. subjects may take part in the study and decline to hand out flyers to people they know.

Subjects who report no recreational drug use other than marijuana at the time of phone screening but then test positive for recreational drug use other than marijuana at the first in-clinic visit will not be reimbursed. Subjects will be informed of this policy at the time of telephone screening. This measure is in place to prevent subjects from lying about no recreational drug use in order to receive compensation for a single visit in this study.

10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 Definitions

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;

(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

10.2 Safety Review

Both the risks listed in Section 6.1 and unknown risks will be monitored as follows:

Adverse events will be monitored from the time of study enrollment until the end of participation. Adverse events will be monitored by medical staff using the "adverse events" CRF. Adverse event monitoring will be conducted at a mid-week call during both titration periods. Adverse events will also be assessed on the alcohol self-administration challenge days. Subjects will be given a wallet card with a 24/7 telephone number in the event that there are adverse effects which the subject would like to consult with medical staff prior to the next scheduled visit. Adverse events will be assessed if at any point in the study a subject uses this

24/7 emergency phone contact. If a subject has an ongoing SAE or unanticipated problem at the time that the subject completes all study procedures, Adverse Event assessment will continue until satisfactory resolution (either resolved or stabilized and is not expected to resolve in the near term) of the event or problem.

For each recorded AE or SAE, the study MD staff or study nurse will assess expectedness based on the known published side effect profile for lacosamide. The study MD staff or study nurse will also assess severity based on the following criteria:

Mild:	An event that is usually transient, requiring no special treatment, and does not generally interfere with the subject's daily activities.
Moderate:	An event that interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. The event is usually ameliorated with additional specific therapeutic intervention.
Severe:	An event that interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the subject and hospitalization may be required, and typically requires intensive therapeutic intervention.
Life-threatening	An event that puts the subject into imminent risk of death without intervention.

The study MD staff or study nurse will assess AE/SAE relationship to the investigational product based on the following criteria:

Unrelated:	The subject did not receive the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE.
Unlikely:	There is evidence of exposure to the investigational product or there is another more likely cause of the AE/SAE.
Possible:	There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause.
Probable:	There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause.
Definite	There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class.

10.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

10.4 Stopping Rules

There are no interim analyses planned that would allow for a determination of futility or overwhelming benefit. Study enrollment will be suspended under the following circumstances:

1. Serious Adverse Events. Study enrollment will be suspended in the event of a single serious adverse event that is determined to be unexpected and at least possibly related. If suspended, study recruitment will not continue until a determination has been made about whether the known risks of participation have changed and the BU Medical Campus/Boston Medical

Center IRB has made a finding that the risk/benefit ratio remains favorable given the possible newly identified risk.

2. Risk of intoxication. Subject recruitment will also be suspended if more than one subject of the first ten subjects enrolled is discontinued by the investigator due to intoxication during the alcohol self administration trial. Due to differences in alcohol tolerance, BAL is not a reliable measure of subjects potentially posing a safety risk. Medical staff will make a subjective determination of risk based on the subject's behavior. After 10 subjects have been enrolled, the trial will be suspended if there are more than 10% of subjects whose participation has been halted by the study team due to concerns about physical safety because of intoxication during the alcohol self-administration trial. If suspended for this reason, the study team will consider design changes to reduce the likelihood of this as a potential risk to study subjects. Recruitment would

resume when the BU Medical Campus/Boston Medical Center IRB has made a determination that proposed changes to the study design have an acceptable risk/benefit ratio.

11 Data Handling and Record Keeping

11.1 Confidentiality

All staff will be fully trained in the procedures for protection confidential health information. To maintain subject confidentiality, study data will be coded on CRFs that are identified by a subject number only. Source records with identifying information and CRFs will be stored in double-locked space with access only by authorized staff. Data stored in the REDcap system have strong protections including file encryption and password access. Subject information will not be released without written permission. Upon approval of the study by an IRB, an application will be filed with NIAAA for a Certificate of Confidentiality.

11.2 Source Documents

Source documents in this study include:
Laboratory test results
Photocopies of the urine drug screening test result
ECG tracings
Subject locator form
Subject contact form

Data generated by the methods described in the protocol will be recorded in the subjects' source binder. Data may be transcribed legibly on CRFs for each subject or directly inputted into an electronic system or any combination thereof.

11.3 Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, a written explanation will be included to detail why the data was not recorded. If the item is not applicable to the individual case, a notation will be made. All entries on will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered closely to the original data. All such changes will be initialed and dated. There will be no erasures or white-out on CRFs. For clarification of illegible or uncertain entries, the clarification will be printed near the item, then initialed and dated. Electronic CRFs in the REDcap system will include an audit trail.

The CRFs that will be used in this study are:
Demographics
Concomitant Medications

Adverse Events
Birth Control Assessment
Urine Drug Screening
Vital Signs
Blood Alcohol Level
Time-line Follow-back
Pregnancy test
Birth control assessment
Medical History
Physical Examination
MINI diagnoses summary
Medication Compliance log
Eligibility
ECG
C-SSRS
CIWA-AR
OCDS
AUQ
VAS
COWAT
Digit Span

11.4 Study Records Retention

Study records will be retained for at least seven years after completion of the study.

12 Statistical Plan

12.1 Study Hypotheses and Planned Analyses

For our primary outcomes, separate analyses will be conducted on data collected during the Priming and Self-Administration periods of the test session.

Hypothesis	Planned Analyses
1. Subjects will consume less alcohol during an alcohol self-administration trial when receiving lacosamide compared to when they are receiving placebo.	The volume of alcohol consumed during alcohol challenge trials 1 and 2 will be used to test the effect of lacosamide on alcohol consumption. We will use a mixed models repeated measures approach to test for differences between alcohol consumed between the lacosamide and placebo self-administration trials[61-62]. This data will be divided into first and second-hour blocks of self-administration. Within-subject factors for this analysis will include treatment and Time Block. Trial order will be used as covariate in these analyses to allow evaluation as to whether the order of treatments had a significant effect on the outcome. Appropriate covariance structures will be determined using Akaike's information criteria to evaluate the best model fit. Results analysis will be examined for both treatment effects and the Treatment x Time Block interaction results.
2. Subjects will report lower levels of craving as measured by the Visual Analog Scale (VAS) and the Alcohol Urge questionnaire (AUQ) during the lacosamide self-administration trial compared to the placebo self-administration trial.	Craving measures (AUQ and VAS) collected at 30-minute intervals during the self-administration trials will be used to test the effect of lacosamide on alcohol craving. A mixed models approach will be used to test for differences in craving between the lacosamide and placebo self-administration trials. Within-subject factors for this analysis will include Treatment and Time Block. Trial order will be used as covariate in these analyses to allow evaluation as to whether the order of treatments has a significant effect on the outcome.
3. There will be no significant difference in verbal fluency or working memory between trials of lacosamide and placebo.	COWAT and Digit Span scores collected on the day of each self-administration trial (prior to consumption) will be used to determine the effect of lacosamide on verbal fluency and working memory. A mixed model repeated measures approach will be used to test for differences in COWAT and digit span scores between the lacosamide trial and the placebo trial. Day and Treatment will be treated as within-subject factors.
4. Subjects will report lower levels of craving and consumption during lacosamide administration as compared to placebo administration.	The alcohol VAS and the TLFB measurements during the seven-day period of medication titration will be used to determine the effect of lacosamide on craving and consumption. Mixed Models repeated measures approach will be used to test for differences in craving and consumption between the lacosamide and placebo trials. Treatment will be used as within-subject factor. VAS measures taken on each of the seven days of medication titration, repeated measures mixed models analysis will be conducted with Day and Treatment as within-subject factors.

12.2 Sample Size Determination

In our initial proposal a group size of 20 completers was selected for use in this study based on an assumed effect size of 1.00 suggested by similar alcohol self-administration studies with amount consumed as the primary outcome[38,63]. This effect size is in the range we found for the anticonvulsant drug zonisamide used in an alcohol self-administration study[37]. For an estimated reduction of 2.1 drinks with an estimated standard deviation (1.48) of the period differences for each participant with each sequence, effect size of this magnitude (1.00) requires a sample size of 20 that would allow for detection of a significant within-subject difference in alcohol consumption with an alpha value of 0.05 and power value of 0.8.

In response to reviewers' concerns about the need to detect a smaller than large effect size we determined the sample size need to detect a moderate effect size (f = 0.25). Assuming a correlation among repeated measures of 0.6 and that the assumption of compound symmetry holds, for comparison of total drinks obtained at 2 time points, for a power of 0.8, with an alpha value of 0.05, a sample size of 28 subjects would be needed for the detection of a moderate effect size. The power using this sample size will be greater than 0.8 if data for 4 time points are analyzed.

Given that this a laboratory based experiment we do not plan to conduct any planned interim analyses in this study.

13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. A copy of the initial IRB approval letter will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

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15. Appendix A: Schedule of Events

	Baseline (May be split over 2 visits)	**Randomization**	**Trial 1**	**Dispense**	**Trial 2**
Clinic Visit #	**0**	**1**	**2**	**3**	**4**
Informed Consent	X				
Urine Drug Screen[A]	X	X	X	X	X
Locator Form	X				
Demographics	X				
Medical History	X				
Physical Exam	X				
MINI V 6.0	X				
Clinical Hematology and Chemistry BUN, Ca, CO2, Cl, Cr, G K, Na, Triglycerides, AST, ALT, GGT, Tbili	X				
Urinalysis	X				
COWAT, Digit Span, Spatial Span			X		X
Vital Signs, weight, Blood Alcohol Level[b]	XX	X	X	X	X
ECG	X				
Prior and Concomitant Meds	X	X	X	X	X
CIWA-AR	X	X	X	X	X
Eligibility Checklist	X				
Drug compliance/accountability			X		X
Urine Pregnancy Test	X	X	X	X	X
Birth control assessment	X	X	X	X	
AEs	X	X	X	X	X
C-SSRS	X	X	X	X	X
Dispense medication/placebo		X		X	
Brief Telephone Interview		**Mid-week call 3-4 days after starting medication**		**Mid-week call 3-4 days after starting medication**	
Treatment Referral					X
TLFB (28 day at baseline)	X	X	X	X	X
VAS		X	X	X	X
OCDS		X	X	X	X
AUQ		X	X	X	X

A) Test for opioids, cocaine, amphetamines, methamphetamine, tetrahydrocannabinol (THC), barbiturates, oxycodone, buprenorphine, methadone and benzodiazepines.
B) if the baseline visit is split between two days, vitals, breathalyzer, and weight are to be taken at each visit.

16. Appendix B: Schedule of assessments during the alcohol challenge

	Observation	Self-admin Block1	Self-admin Block2
Assessment			
BAC	**Every 10 minutes**	**Every 30 minutes**	**Every 30 minutes**
VAS[a)]	**Every 10 minutes**	**Every 30 minutes**	**Every 30 minutes**
AUQ		**Every 30 minutes**	**Every 30 minutes**