BRAIN MECHANISMS OF TOPIRAMATE'S EFFECTS ON HEAVY DRINKING

Regulatory Sponsor: *Reagan Wetherill, Ph.D.*
Psychiatry
3900 Chestnut Street
Philadelphia, PA 19104
(215) 222-3200 ext. 141

Funding Sponsor: *Departmental Funds (Kranzler)*
Contact Person: Linda L. Mangino
Manager of Administration & Finance
CSA/Psychiatry
University of Pennsylvania
3440 Market Street, Ste. 370
Philadelphia, PA 19104
(484) 802-4375

Study Product: *Topiramate*

Protocol Number: *818988*

Version 9: [10/10/2014]

Table of Contents

Study Summary

Title	BRAIN MECHANISMS OF TOPIRAMATE'S EFFECTS ON HEAVY DRINKING
Short Title	Brain Mechanisms of Topiramate
Protocol Number	*818988*
Phase	N/A
Methodology	Pilot study/Basic Research
Study Duration	Approximately 24 months
Study Center(s)	Single Center, Center for Studies of Addiction
Objectives	1. Pilot test cue sets and confirm brain and behavioral responses to alcohol cues using pseudo-continuous arterial spin labeling functional magnetic resonance imaging 2a. Demonstrate neuromodulatory effects of a GABA/glutamate modulator, topiramate, on resting baseline and alcohol cue reactivity 2b. Examine the mechanism underlying topiramate's ability to blunt alcohol cue reactivity and reduce heavy drinking days
Number of Subjects	100 enrolled for a target of 40 for main study, up to 10 for the pilot sub-study
Diagnosis and Main Inclusion Criteria	DSM-5 diagnosis of Alcohol Use Disorder
Study Product, Dose, Route, Regimen	Topiramate tablets encapsulate for blinding. Maximum daily dosage is 200 mg by mouth. Six-week titration to maximal dosage.
Duration of administration	8 weeks
Reference therapy	placebo
Statistical Methodology	Frequencies and descriptives; Voxel-wise analyses of cerebral blood flow (CBF) data using a general linear model on absolute and relative CBF

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Alcohol is the third leading risk factor for premature death and disability [1], as well as a leading cause of preventable cancers [2]. Alcohol dependence affects 18-20 million Americans (i.e. 1 in 12), and alcohol problems cost our society nearly $225 billion annually [1]. Alcohol dependence is a chronic disorder marked by high rates of relapse. Relapses to drinking are often preceded by a strong desire or craving for alcohol when exposed to alcohol-related stimuli. Knowledge of the mechanisms underlying stimuli- or alcohol cue-induced craving may aid in the search for additional viable pharmacotherapies to help alcohol dependent individuals remain abstinent for life.

Currently, there are three FDA-approved medications to treat alcohol use disorders (AUD): naltrexone, acamprosate, and disulfiram [3]. Empirical evidence suggests that naltrexone reduces the reward properties of and cravings for alcohol [4] and acamprosate supports abstinence [5]; however, their effect sizes compared to placebo are small [6-8]. Disulfiram differs from naltrexone and acamprosate in that it blocks the metabolism of alcohol's primary metabolite, acetylaldehyde, which accumulates in the blood causing unpleasant effects when alcohol is ingested [9]. There is limited evidence of the efficacy of disulfiram, and its potential for toxicity limits it use [10]. These concerns about safety and limited efficacy likely contribute to the fact that FDA-approved medications for AUD are not widely prescribed [7, 11]. Indeed, only 2.8% of patients treated in the Veterans Health Administration who were diagnosed with an AUD received pharmacotherapy [6]. Given these issues and concerns, several medications, other than the currently approved medications for AUD, have been prescribed off label and have shown promise in reducing alcohol consumption.

One promising medication for the treatment of AUD is the GABA/glutamate modulator, topiramate. Although topiramate is FDA-approved as an anticonvulsant, prophylactic treatment for migraine, and for weight loss, both preclinical [12, 13] and clinical studies [14-17] show that topiramate is effective in reducing heavy drinking. Specifically, topiramate reduced alcohol craving [17]; had a moderate treatment effect in reducing heavy drinking in three published placebo-controlled trials [14-16], and appears to have a larger effect size than naltrexone [18, 19] and acamprosate [20]. Kranzler et al. (in press) found that 200 mg/day of topiramate was well tolerated, reduced the number of heavy drinking days and increased the number of abstinent days more than placebo. In fact, during the last week of the 12-week study, the odds of the placebo group having at least one heavy drinking day was 5.33 times that of the topiramate group. Although these robust findings support the use of topiramate to reduce heavy drinking, the mechanisms underlying its therapeutic effects are not well understood. Thus, the present study aims to elucidate the brain and behavioral mechanisms that mediate topiramate's reduction of heavy drinking.

Functional neuroimaging provides a powerful, non-invasive method to study addictive processes. For example, we, and others, have identified a consistent neural substrate for reactivity to cocaine-, heroin-, cigarette-, marijuana- and alcohol-related cues using a variety of imaging modalities [21-26]. In general, chronic, heavy substance users show greater neural activity in reward-related brain regions, such as the orbitofrontal cortex (OFC), striatum, and anterior cingulate cortex, during drug cue exposure than during non-drug cues. Neuroimaging techniques have also been used to determine how some pharmacotherapies influence factors contributing to substance use. For example, naltrexone has been shown to reduce alcohol cue-induced activation in the ventral striatum (VS) and OFC in non-treatment-seeking alcoholics [27], suggesting that naltrexone's effects are mediated through its reduction of reward-related cue reactivity. To date, there are no published studies examining the effects of topiramate on neural activity or how such effects could be associated with changes in heavy drinking. Based on our own recent finding that topiramate decreased heavy drinking days and increased abstinent days and other research indicating that topiramate reduces heavy drinking days [14-16] and self-reported craving [17], we hypothesize that topiramate may be an effective tool in reducing the reward-related neural activity commonly associated with heavy drinking (i.e., alcohol cue reactivity). Further, our longitudinal, quantitative perfusion fMRI approach, which provides

for the acquisition of resting brain cerebral blood flow (CBF: ml of blood/100 g of tissue/minute) will provide invaluable information on the mechanisms underlying the ability of a GABA/glutamate modulator to blunt alcohol cue reactivity and heavy drinking.

Neurogenetics is a promising and novel addition to neuroimaging studies. Twin, family and adoption studies indicate that vulnerability to substance abuse is partially inherited. Individual response to medications will most likely be related to genetic phenotypes. Genetics studies, on their own, require huge sample sizes and are expensive; however, when combined with neuroimaging, which offers a 'picture' of individual brains, we can learn why some individuals are vulnerable to alcohol and substance use disorders and why others do not. For example, evidence suggests that the rewarding properties of alcohol involve GABA-ergic, glutamatergic, opiodergic, and dopaminergic neurotransmitter systems. As such, we will focus on genes associated with these systems, such as *DRD4* (D4 dopamine receptor gene), *GABRA2* ($GABA_A$ receptor alpha-2 subunit gene), *OPRM1* (mu-opioid receptor gene), and *GRIK1* (glutamate receptor, ionotropic, kainate 1 gene) [28]. Further, based on our previous research showing that the C-to-A single nucleotide polymorphism (SNP), rs2832407, in intron 9 of the *GRIK1* gene is associated with alcohol dependence [29], this variant in *GRIK1* will be our primary focus. Thus, those who have the A allele will likely show the strongest alcohol cue responses.

In summary, the data reviewed above provide strong support for the need to identify the brain and behavioral mechanisms underlying the effects of one of the most prescribed [30], yet poorly understood, medications to treat AUD, topiramate, on key factors contributing to heavy drinking. Given that topiramate 1) has been shown to be effective in reducing heavy drinking [14-17], 2) appears to have a larger effect size than naltrexone [18, 19] and acamprosate [20], and 3) has dual $GABA_A$-mediated inhibitory impulses and AMPA and kainate antagonist effects [31] that likely suppress reward-related mesocorticolimbic dopamine release, we hypothesize that topiramate ameliorates neurophysiological vulnerabilities to heavy drinking by dampening neural activity in the brain at rest *and* during alcohol cue exposure in reward-related brain regions. The current study will elucidate the brain and behavioral mechanisms underlying topiramate's effects and test our hypotheses using a randomized, double-blind placebo-controlled design, pseudo-continuous arterial spin labeling (pCASL) perfusion functional magnetic resonance imaging (fMRI), and other relevant assessments described below. This project will yield novel findings on brain and behavioral responses to alcohol cues, the neuromodulatory effects of topiramate on alcohol cue reactivity, and the mechanisms [resting baseline (RB) modulation] underlying the ability of this GABA/glutamate modulator to blunt alcohol cue reactivity and heavy drinking. Thus, the proposed research, although <u>not a treatment trial</u>, will examine the effects of topiramate on brain and behavior and thereby contribute to medications development and the treatment of AUD.

1.2 Investigational Agent

Topiramate is an anticonvulsant medication for oral administration approved in the United States for the treatment of seizures and to prevent migraine headaches in adults. The molecular formula is C 12 H 21 NO 8 S and the molecular weight is 339.35. It is designated chemically as 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate. Preclinical studies indicate that topiramate blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainite subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV. Topiramate absorption is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The bioavailability of topiramate from the table formulation is about 80% compared to a solution and is not affected by food. The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady-state is reached in about 4 days.

According to the FDA-approved labeling, topiramate has been found to be safe at doses of 200mg and 400mg per day in adults.

1.3 Preclinical Data

<u>Drug-Drug Interactions and Precautions</u>

Topiramate may have interactions with some antiepileptic drugs and oral contraceptives. Specifically, concomitant use of topiramate with standard antiepileptic drugs (i.e., Phenytoin, Carbamazapine, Valproic acid, and Lamotrigine) has been shown to decrease plasma levels of topiramate. Topiramate may also reduce the efficacy of some hormonal contraceptives (birth control pills, hormonal implants, or hormonal injections). Topiramate does not produce clinically significant additive central nervous system depressant effects in combination with ethanol. Concomitant use of topiramate with other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide, or dichlorphenamide) may increase severity of metabolic acidosis and may also increase the risk of kidney stone formation. There is no evidence that topiramate has carcinogenic, teratogenic, or mutagenic potential. Further, topiramate is not reinforcing and is therefore not a drug of abuse.

1.4 Clinical Data to Date

Topiramate has been evaluated for safety in over 3000 adults, and there are few serious adverse effects associated with topiramate. The most common adverse effect of topiramate compared to placebo is numbness and tingling (49% vs. 6%). The other most common side effects (experienced by 10-31% of patients) in clinical trials include: change in sense of taste, tiredness/sleepiness, fatigue, dizziness, loss of appetite, nausea, diarrhea, weight decrease, difficulty concentrating and difficulty with memory. Cognitive dysfunction adverse effects (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties) that were reported during 6-month migraine prophylaxis studies (28% vs. 10% for placebo) were of mild-to-moderate severity. Other adverse effects (experienced by 5-9% of patients) in some clinical trials include: nervousness, slow thinking, abnormal vision, confusion, decreased sensitivity (hypesthesia), anxiety, abdominal pain, dry mouth, involuntary muscle contractions, and language problems. Depression and mood problems have also been reported (experienced by 5-9% of patients). Severe metabolic acidosis (decreased bicarbonate levels) is associated with topiramate treatment in 3-7% of individuals taking the medication.

1.5 Dose Rationale and Risk/Benefits

Dose Rationale

The dosage of topiramate selected for this study (200 mg/day) is based on previous research indicating that 200 mg/day is the dosage at which heavy drinkers begin to show therapeutic effects [14-16]. Further, one study of 138 heavy drinkers who sought to reduce their drinking received a 12-week treatment with topiramate (N=67) 200 mg/day or matching placebo and showed that topiramate was well tolerated, with no serious side effects, and was efficacious at reducing heavy drinking days and increasing abstinent days [32].

Potential Risks

The potential risks of this study include adverse reactions to topiramate, adverse reactions attributable to the combination of topiramate and alcohol, and the small risk incurred by venipuncture. Individuals will be advised to drink adequate amounts of liquid to avoid renal calculi (experienced by 2% of individuals taking the medication). Individuals who are taking carbonic anhydrase inhibitors will be excluded from the study, due to the added risk of metabolic acidosis (decreased bicarbonate levels), which has been reported in 3-7% of individuals taking the medication.

Topiramate is not reinforcing and therefore there is no abuse potential; however, access to topiramate will be strictly limited by the study design and use will be carefully monitored.

Potential Benefits

Individuals receiving study medication may experience a reduction in or discontinuation of their alcohol consumption, which may improve their health and well-being. Subjects will also receive close psychiatric and medical attention, including careful evaluation of their medical and psychiatric status. The potential benefits to society include a potential improvement in the effectiveness of treatment for problem drinking, which may reduce the personal and societal costs associated with the problem.

Risk Benefit Ratio

The potential benefits of this study far outweigh the potential risks. Alcohol use disorders are serious disorders with mildly effective pharmacotherapy. Even in the best programs, relapse rates are high. Individuals accepted into this study will receive close medical and psychiatric monitoring. Subjects will be screened prior to admission into the study and those at risk for adverse reactions will be excluded. Subjects selected for participation will be monitored closely for adverse effects of topiramate.

2 Study Objectives

Objective 1 Pilot cue sets (see Appendix 1) and confirm brain and behavioral responses to alcohol cues in individuals with AUD using pCASL fMRI

Hypothesis 1: Similar to our other pCASL fMRI cue-reactivity studies in drug-dependent individuals, subjects will exhibit greater brain activity in the interconnected VS and medial orbitofrontal cortex (mOFC) during alcohol cue exposure compared to non-alcohol cue exposure.

Objective 2a Demonstrate neuromodulatory effects of a GABA/glutamate modulator, topiramate, on RB and alcohol cue reactivity

Hypothesis 2a: We hypothesize that topiramate will ameliorate neurophysiological vulnerabilities by dampening neural activity in the brain 'at rest' *and* during alcohol cue exposure in reward-related regions, such as the amygdala, mOFC, VS, and the insula. In contrast, neural activity in placebo-treated individuals at rest and in alcohol cue reactivity will not differ from pre- to post-treatment.

Objective 2b Examine the mechanism underlying topiramate's ability to blunt alcohol cue reactivity and reduce heavy drinking days

Hypothesis 2b: We hypothesize that there will be a direct relationship between RB in the VS and mOFC and its effects on alcohol cue reactivity. Although overall effects are expected, reductions in heavy drinking days will correlate with topiramate's ability to modulate reward circuitry responses.

Exploratory Objective Examine the moderating effects of rs2832407 on topiramate's effects on brain and behavioral responses

Exploratory hypothesis: C-allele homozygotes at this locus will show the most robust effects of topiramate.

3 Study Design

3.1 General Design

- ***Phase IV Study -*** This is a phase IV research study aimed at identifying the brain and behavioral mechanisms underlying the GABA/glutamate modulator, topiramate.
- ***Design –*** Heavy drinkers who meet DSM-5 criteria for AUD and express an interest in reducing or stopping drinking will be recruited, screened, consented, and if eligible, will complete a randomized double-blind, placebo-controlled study of topiramate (*N*=40; topiramate 200 mg/day: *n*=20 or placebo: *n*=20). Topiramate or placebo will be initiated after Scan 1 and continued with weekly visits and medical management [33]. During the 7th week, participants will complete Scan 2 followed by medication taper and an endpoint visit. We will use perfusion fMRI during alcohol cue exposure to acquire brain and behavioral responses to alcohol cues. The goals of this study are to pilot test the validity of our alcohol cues and to identify brain and behavioral mechanisms of topiramate in reducing heavy drinking in alcohol dependent individuals.
- ***Study Duration –*** The duration of this study will be approximately 9 weeks, including screening, Scan 1, 8 weeks of medication and medical management (including medication taper), Scan 2 during week 7, medication taper, and an endpoint visit. The entire study will run for approximately 24 months.

3.2 Primary Study Endpoints

The primary endpoints to be measured include:

- Self-report ratings of cues, subjective ratings of craving during/following cue exposure, and neuroimaging data on cerebral blood flow when the brain is at rest and when exposed to alcohol cues.

3.3 Secondary Study Endpoints

The effects of rs2832407 on topiramate's neural mechanisms

4 Subject Selection Subject Selection and Withdrawal

4.1 Inclusion Criteria

1) Physically healthy, as determined by a comprehensive physical examination and approval of the study physician males or females who drink alcohol, ages 18-60.
2) Have an average weekly ethanol consumption of ≥24 standard drinks for men, or ≥18 standard drinks for women [34].
3) Females must be non-pregnant, non-lactating and either be of non-childbearing potential (i.e. sterilized via hysterectomy or bilateral tubal ligation or at least 2 years post-menopausal) or of child bearing potential but practicing a medically acceptable method of birth control. Examples of medically acceptable methods for this protocol include: the birth control pill, intrauterine device, injection of Depo-Provera, Norplant, contraceptive patch, contraceptive ring, double-barrier methods (such as condoms and diaphragm/spermicide), male partner sterilization, abstinence (and agreement to continue abstinence or to use an acceptable method of contraception, as listed above, should sexual activity commence), and tubal ligation.
4) Provide voluntary informed consent.
5) Must be able to read. [Subjects are required to be able to read because there are several self-administered measures that they must read, understand and provide written answers.]
6) Intelligence quotient of ≥ 80, as estimated by the 2-subtest score of the Wechsler Abbreviated Scale of Intelligence (WASI) [35].

4.2 Exclusion Criteria

1) A current, clinically significant physical disease or abnormality on the basis of medical history, physical examination, or routine laboratory evaluation.
2) History of head trauma or injury causing loss of consciousness, lasting more than five (5) minutes or associated with skull fracture or inter-cranial bleeding or abnormal MRI.
3) Current major DSM-IV Axis I diagnoses other than alcohol, nicotine, and cannabis use disorders.
4) Presence of magnetically active irremovable prosthetics, plates, pins, permanent retainer, bullets, *etc*. (unless a radiologist confirms that it's presence is unproblematic).
5) History of a serious psychiatric illness including psychosis, bipolar disorder, or suicidal or homicidal intent.
6) Current treatment with carbonic anhydrase inhibitors, due to the added risk of metabolic acidosis.
7) Claustrophobia or other medical condition preventing subject from lying in the MRI for approximately one (1) hour.
8) Current regular treatment with psychotropic medications (e.g., benzodiazepines, antidepressants), which affect neurotransmitter systems or a medication being used to treat alcohol use disorders (e.g., naltrexone, acamprosate).
9) Vision problems that cannot be corrected with glasses.
10) Body Mass Index (BMI) greater than or equal to 34, body girth greater than 52 inches and a head girth greater than 25 inches [Imaging data acquisition is impaired with high weight individuals].

11) Individuals suffering from or with a history of stroke and/or stroke related spasticity.
12) History of glaucoma or kidney stones.
13) Individuals who are HIV positive, as the human immunodeficiency virus affects the brain.
14) Individuals with a history of seizures.
15) Individuals who have taken topiramate for alcohol use disorder and report no treatment response.
16) Current DSM-5 diagnosis of alcohol use disorder that is clinically too severe to permit them to participate in a research trial in which the goal is to stop or reduce drinking [Because there is no clear empirical basis for choosing a cutoff with respect to AUD criteria, we will exclude patients who, on clinical examination by a physician, are deemed to be too severely alcohol dependent to permit them to participate in a research trial. This determination will be based on evidence of adverse medical (e.g., gastritis) or psychiatric effects (e.g., depression with suicidal ideation). In addition, individuals with no recent evidence of the capacity to reduce drinking from very high levels of intake or a history or present evidence of significant alcohol withdrawal symptomatology will be excluded. (Significant withdrawal will be considered to be present when there is a history of substantial tremor, autonomic changes, perceptual distortions, seizures, delirium, or hallucinations or a report of drinking to avoid withdrawal symptoms or of prior treatment of withdrawal).

4.3 Subject Recruitment and Screening

Subjects will be recruited from those who respond to IRB-approved advertisements. Advertisements will be in the form of IRB-approved radio ads, flyers, billboards, e-lists, and word of mouth. Individuals who have completed prior studies and meet study criteria will also be invited to participate if subject participation ended at least 30 days before the current study starts (i.e., no pharmacotherapy or psychotherapy for 30 days). An initial telephone interview covering recent medical status, substance use, treatment history, medication, and general psychiatric history will be conducted. The potential subject will be provided with an overview of the study and will be informed that all information obtained will be used to determine his/her eligibility for study participation. If the individual satisfies preliminary criteria and shows continued interest in participating in the study, an appointment will be made for further screening at the Center for Studies of Addiction (CSA). The CSA initial screening process will be described, and the individual will also be informed that s/he must be available for at least two separate appointments during the screening week (unless the two appointments are combined). For details on Screening, see 6.2 Informed Consent and Screening Visit below.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects with severe psychological symptoms (e.g., suicidal thoughts), those who fail to adhere to protocol requirements, and those withdraw consent will be withdrawn from the study and if applicable, referred for appropriate clinical care. If a subject is found to be pregnant during screening or during study, she will immediately be withdrawn from the study, referred for obstetric evaluation, and advised to discontinue all drinking.

Any subject experiencing a serious adverse event felt to be related to study drug should be withdrawn from the study.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

We will make a strong effort (via phone calls and alternative contact information) to obtain follow-up information on all subjects who are prematurely withdrawn from the project.

5 Study Drug

Topiramate is an anticonvulsant medication for oral administration approved in the United States for the treatment of seizures and to prevent migraine headaches in adults. According to the FDA-approved labeling, topiramate has been found to be safe at doses of 200mg and 400mg per day in adults.

For more detailed information, see section 1.2 (Investigational Agent).

5.1 Description

Topiramate for this study is supplied in opaque capsules. The placebo formulation is a table that appears identical to the topiramate capsules.

5.2 Treatment Regimen

Subjects will be randomized to receive topiramate or placebo, to begin after completing the first Laboratory/MRI visit according to the following regimen:

Table 1. Medication Dosing Schedule for Topiramate

	Medication Dispensed	Morning Dose	Evening Dose	Total Daily Dose
Screening Visit -0	Week 0	No medication	No medication	0 mg
Scan 1/ Visit 1	Week 1	No medication	25 mg	25 mg
Visit 2	Week 2	25 mg	25 mg	50 mg
Visit 3	Week 3	25 mg	50 mg	75 mg
Visit 4	Week 4	50 mg	50 mg	100 mg
Visit 5	Week 5	50 mg	100 mg	150 mg
Visit 6	Week 6	100 mg	100 mg	200 mg
Scan 2/Visit 7	Week 7	100 mg	100 mg	200 mg
Taper Visit 8	Week 8	Reduce dose by 50 mg every 2 days (150 mg for 2 days, 100 mg for 2 days, 50 mg for 2 days, then D/C		
Final visit/Visit 9	Week 9	No medication	No medication	0 mg

If subjects experience significant side effects from the study drug (topiramate or placebo), the investigators will have the option to reduce the dose (number of pills) during the study, based on consultation with the research staff, or as clinically indicated, by interviewing the subject directly. All dosing is on a double blind basis, thus, the physician can vary the number of capsules of placebo or topiramate in response to adverse effects reported by the subject. Upward titration following a dose reduction will be allowed once during the trial. Dose titration, if necessary, will be carefully documented in the study chart along with the clinical rationale.

5.3 Method for Assigning Subjects to Treatment Groups

Subjects will be randomly assigned to one of two treatment conditions: topiramate 200 mg/day (n = 20) or placebo (n = 20). Study staff and the Investigational Drug Service (IDS) staff will be responsible for medication randomization. The process for randomization is: 1) Research coordinator will complete an "randomization form," which includes the variables to be entered into the block randomization program by study staff (i.e., sex, number of heavy drinking days in the past month(>12 heavy drinking days and =<12 heavy drinking days)); 2) study staff will enter variables into the block randomization program, 3) study staff will fax randomization group to IDS, who will assign a kit number to subject and fax kit assignment to research coordinator; 4) the research nurse or Physician will dispense medication to subject and complete and sign IDS Rx prescription form included in starter kit. 5) Research coordinator will fax completed form to IDS. The medication will be dispensed using the above dosing schedule. To maintain double-blind conditions, study staff responsible for randomization will not be involved in subject participation, study visits, or data collection.

Study drug for subsequent visits will be ordered by the research coordinator using the "Research Pharmacy Schedule" form, a copy of which will be retained in the subject's research file. At each visit, a supply of

study drug will be dispensed by the research nurse. Subjects with severe psychological symptoms or determined to be inappropriate for the study by an investigator will be withdrawn from the study. Subjects who are withdrawn completely will be referred for appropriate clinical care.

5.4 Preparation and Administration of Study Drug

Topiramate will be purchased commercially and formulated in opaque capsules by IDS. Placebo will be formulated to match the active medication, such that inspection of the capsules will not permit the two to be differentiated. The study medication will be shipped to the Research Pharmacy where, it will be stored at room temperature (59-86º F) until dispensed to nursing staff for distribution to subjects. The IDS will supply study staff with starter kits for week 1 doses. Study medication will be stored at room temperature (59-86º F) in a locked drawer until dispensed by nursing staff for distribution to subjects.

5.5 Subject Compliance Monitoring

We will conduct pill counts at the weekly visit of all study subjects. Unused amounts will be documented. Proper drug dosing will be reviewed with subjects at each visit with clear instructions to take all study drug, as directed. In addition, subjects in both medication groups will receive Medical Management (MM) [33]. This provides a basic clinical intervention that was designed to be used in conjunction with prescribed medication, and to be easily implemented by medically trained practitioners in non-specialty settings. The treatment will support subjects' efforts to reduce their drinking, with the study nurse making direct recommendations for reducing drinking to sensible levels (see below).

5.6 Prior and Concomitant Therapy

Individuals who have completed prior alcohol treatment studies and meet study criteria will also be invited to participate if subject participation ended at least 30 days before the current study starts (i.e., no pharmacotherapy or empirically supported treatment for 30 days). Subjects currently in treatment program for alcohol use disorders. See exclusion criteria, section 4.2.

5.7 Packaging

The Investigational Drug Service of the University (IDS) of Pennsylvania will package bulk drug on-site, as containing 8 days of medication in child-safe prescription bottles. Subjects will be provided with an extra day of medication to ensure that subjects have enough medication if a weekly visit needs to be rescheduled.

5.8 Blinding of Study Drug

All subjects and research staff will be blinded as to whether the subject is in the topiramate or placebo group until the end of the study once the decision to break the study blind is determined (after study database lock). Codes linking randomization number for each subject to actual treatment will be secured in a sealed, opaque envelope and maintained in a locked drawer in the research pharmacy and the hospital pharmacy. Research subjects will be given the emergency contact number for the study during the consenting process.

See section 8.4 (Unblinding Procedures) for a description of the process for unblinding a study subject.

6 Study Procedures

6.1 *Initial Telephone Screen (*approximately 20 minutes)

Subjects will be recruited from the Center for Studies of Addiction at 3900 Chestnut St. through local advertisements. Subjects who express interest by responding to advertising are contacted by phone and participate in a telephone screening interview. The nature of the study, including the number of visits to the center and a description of fMRI procedures, subject protections and confidentiality, are described. If the caller is still interested, questions on general health are asked. If the applicant is determined to be eligible based on this screening, s/he is asked whether they accept or decline to participate. If the caller is still interested, s/he will be scheduled for an initial consenting appointment.

6.2 *Informed Consent and Screening Visit* (approximately 4 hours)

Upon arriving to the Informed Consent and Screening Visit, subjects will be asked to show legal identification and to complete a breathalyzer test to ensure a breath alcohol concentration (BrAC) of 0.00 g%. Reading ability will be evaluated followed by a review of HIPAA privacy laws and the informed consent. Specifically, subjects will be provided a standard HIPAA form that contains privacy laws, and a study staff member will review the consent form with the subject, including an explanation of the study protocol, its risks, potential benefits, and alternative treatment. Following resolution of any questions, subjects who appear to understand the nature of the study and consent will be asked to sign the study consent form. An entire copy of the informed consent form will be given to each subject. S/he is also reminded that the consent expresses willingness to participate but that the subsequent screening process will determine final eligibility. Further, s/he is reminded that participation is voluntary, and at any time, s/he may withdraw from the study.

Following consent, subjects will watch an fMRI video that simulates the experience of undergoing an MRI, meet with the study nurse to complete physical examination and laboratory evaluation, and meet with study staff to complete additional assessments. Baseline laboratory measures include: 1) CBC, 2) Blood chemistries (i.e., standard blood work and lipids), 3) gamma glutamyltransferase (GGTP) to assess the validity of self-reported drinking, 4) HIV test (blood), 5) Electrocardiogram, 6) Urine Toxicology (presence of psychoactive drugs) and 7) for females: a urine pregnancy test and an additional blood sample for biochemical measurement of progesterone and estradiol levels for determination of menstrual cycle phase. A total of approximately 3 tablespoons of blood will be taken. A portion (approximately 2 tablespoons) of this blood sample will also be used to acquire DNA samples from each subject. This portion will be stored for later extraction and analyses. In cases where blood samples are drawn and potential lab errors or abnormal findings occur, subjects will be asked to provide an additional blood sample to repeat the test(s). If the HIV test is positive, the subject will be referred to their primary care provider.

Measures obtained:

a. *Sociodemographic/subject information:* General demographic information, marital status, educational, and occupational information will be obtained.

b. The **Timeline Follow-back (TLFB)** [36] will be used to estimate past 30-day drinking. 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. We will also measure tobacco and other substance use patterns using the TLFB.

c. The **Short Index of Problems (SIP)** is a 15-item instrument, derived from the 50-item DrInC [37], measures alcohol dependence symptoms and medical, psychological, social, occupational, and legal problems. We have chosen to use the shorter SIP because we [38] found that, like the DrInC, the SIP measures a single factor of alcohol-related problems.

d. The **Alcohol Urge Questionnaire (AUQ)** [39] is an 8-item, self-administered state measure assessing the urge for an alcoholic drink at the time the questionnaire is completed and provides an index of acute craving. The AUQ contains four items pertaining to the desire for a drink: two items regarding expectations of positive effects from drinking, and two items relating to the inability to avoid drinking if alcohol were present. This measure has strong correlations with measures of alcohol dependence and severity.

e. The **Fagerstrom Test for Nicotine Dependence (FTND)** [40] is a 6-item, self-report measure of nicotine dependence derived from the Fagerstrom Tolerance Questionnaire.

f. The **Obsessive Compulsive Drinking Scale (OCDS)** [41] is a 14-item, self-report measure that assesses aspects of alcohol craving, including obsessive thoughts about alcohol use and compulsive behaviors toward drinking.

g. The **Clinical Institute Withdrawal Assessment for Alcohol Scale – revised (CIWA-Ar)** [42] is a 10-item scale for clinical quantification of the severity of alcohol withdrawal.

h. **Structured Clinical Interview for DSM (SCID)** will be administered to obtain DSM-5 diagnosis of alcohol use disorder and, using DSM-IV criteria, to rule out other psychiatric disorders (except nicotine and cannabis use disorders).

i. **Wechsler Abbreviated Scale of Intelligence (WASI)** [35] is a brief and reliable measure of intelligence that provides an estimate of an individual's IQ scores. We will use the two-subtest form

(vocabulary and matrix reasoning) that offers an estimate of an individual's cognitive functioning. Individuals with an intelligence quotient of ≤ 80 are excluded because they do not have the cognitive skills necessary to participate in several of the study components.

j. **Beck Depression Inventory (BDI)**, a 21-item self-report measure of depressive symptoms, yields a total score that ranges from 0 to 63 (Beck et al. 1961). The BDI is generally regarded as a sensitive self-report measure of depressive symptoms and suicidal ideation.

k. **Menstrual Cycle Questionnaire (MCQ)** is a questionnaire administered by the Nursing Staff to all prospective female subjects that elicits information on menses status, menstrual cycle length, and premenstrual symptoms (PMS). This measure is acquired because hormone levels vary and cortical GABA levels decline from follicular to luteal phase of the menstrual cycle [43], and these changes influence CBF [44] and behavior [45]. Thus, this questionnaire (and progesterone/estrogen levels) will help us determine if females are pre-, peri- or post-menopausal.

ALL screening assessments will be performed to determine subject eligibility criteria, which will be documented. All subjects will also complete a practice round of cognitive testing with the CogState battery (described in detail below). The PI will confirm and sign off on the inclusion and exclusion criteria on a case report form (CRF) prior to the subject formally included in the study. Prospective subjects will be notified of their eligibility by telephone within 5 business days. This waiting period is necessary to examine results from the screening visit to determine whether the subject meets eligibility requirements.

6.3 Laboratory/MRI Session 1 Visit (approximately 3.5 hours)

Interested, eligible, consented subjects will attend the first of two laboratory/MRI session visits. Prior to each scan visit, subjects will be instructed not to drink alcohol for 24 hours before the scheduled scan session. Upon arrival, subjects will be breathalyzed to ensure that they have not recently consumed alcohol (BrAC = 0.00 g%). During this visit, subjects will complete: 1) brief questionnaires (see Table of Assessments), 2) CogState and CogBias computerized tasks (described below), 3) females will take a urine pregnancy test and provide a blood sample (approximately 2 tablespoons) for biochemical verification of menstrual cycle phase, 4) an MRI scan, and 5) following the scan, a brief medical management session with a nurse to receive medication.

Prior to MRI scanning, subjects will meet with study staff who will conduct the CIWA-Ar and prepare the subject for the MRI session. Subjects will also be asked to drink to satiety prior to starting the scan session to avoid potential confounding effects of thirst on neural responses to cues. During the scanning session, subjects will be asked to lie still with their eyes open for a 5 minute resting baseline scan, followed by two 10-minute audio-visual clips consisting of either alcohol-related cues: individuals differing in race, age and sex who are drinking alcohol and using explicit language designed to induce appetitive desire for alcohol; or non-alcohol-related cues that are similar in content, but individuals relate interesting short stories that do not portray alcohol consumption or alcohol reminders. Subjects will also be asked their level of alcohol craving (on a scale from 0-10) before and after each audio-video clip. Following the scan session, subjects will meet with a nurse to receive their first week of medication and the initial medical management session (see below).

MRI scanning will be conducted on a Siemens 3.0 Tesla Trio whole-body scanner (Siemens AG, Erlangen, Germany), using a standard Transmit/Receive head coil. A 30-second localizer scan and a 5-minute T1-weighted high-resolution scan are acquired before the functional scanning. These scans are used for subsequent normalization and anatomical co-registration of the images, and they provide subjects with a habituation period to the MRI environment. The 3-plane localizer scan (sagittal, axial and coronal) is acquired with FOV = 280 mm, TR/TE = 20/5ms, 192x144 matrix, and slice thickness 5mm. Acquisition parameters for the 3D High-Resolution MPRAGE structural in the axial plane are: FOV = 250 mm, TR/TE = 1620/3ms, 192x256 matrix, slice thickness 1 mm. The CASL technique will be used to acquire images during functional MRI (RB and SC exposure). Interleaved images with and without labeling will be acquired using a gradient echo echo-planar imaging sequence. A delay of 1000 ms will be inserted between the end of the labeling pulse and image acquisition to reduce transit artifact. Acquisition parameters are: FOV=22cm, matrix=64x64, TR/TE = 3000/17ms, flip angle=90°. Fourteen slices (8mm thickness with

1.5mm gap) will be acquired from inferior to superior in a sequential order. Each cue CASL scan with 200 acquisitions will be 10 minutes in length. The RB CASL scan will be 5 minutes with 100 acquisitions.

Double Booking Option
Subjects may be offered the option to "double-book" a scanning appointment for the first scan. In this case, they would be scheduled for a scan as a backup to a participant from other studies conducted by our lab. If the participant from the other study does not arrive for their scheduled scan, our subject will fill that MRI time slot. If our subject is not scanned, they will be compensated for their time and travel and re-scheduled for another scan session. If a subject does opt for double-booking, they would only be double-booked once and only for their first scan.

Assessments on Scan Visits:

CogState computerized battery, which is a 20-minute assessment to examine the cognitive effects of changes in drinking behavior and of topiramate treatment, will be administered at Laboratory/MRI session 1, 2, and endpoint visits. It consists of:

- Detection Task (Psychomotor Speed) [2 minutes]. For this test, subjects must press a response key as soon as they detect an event. The software measures the response time to detect each event.
- Identification Task (Attention) [3 minutes]. In this task an event occurs in the center of the computer screen and the subject must decide whether the event meets a predefined and unchanging criterion. The software measures the speed and accuracy of each response.
- One Card Learning Task (Visual Learning) [5 minutes]. In this task a pre-determined set of six cards is shown repeatedly four times. Each time the set of six cards is presented the six cards are intermixed with eight distracter stimuli. Each distracter stimulus is shown only once in a task. Each time subjects see a stimulus presented in the center of the computer monitor they must decide whether they have seen this card in the task before. The software measures the speed and accuracy of each response.
- One Back Memory Task (Working Memory) [1 minute]: On this task the subject is shown a single stimulus in the centre of the computer screen (a card turns face up). They must decide whether the current card matches the card they had seen on the immediately previous trial. The software measures the speed and accuracy of each response.
- Shopping List Task (Verbal Learning and Memory) [5 minutes]: The test administrator reads the subject a brief list of words at the rate of one word every 2 seconds. After the list is complete, the subject is asked to recall as many of the words as possible. This process is repeated for a second and a third trial. After a delay, the subject is asked again to recall as many words as possible, without being read the list again. The total number of words recalled at initial recall and delayed recall are the outcome scores for this task.
- Groton Maze Learning Test (GMLT) (Reasoning and Problem Solving) [5 minutes]: The task begins with a chase task to familiarize the subject with the task context. The subject is shown a 10 x 10 grid of tiles on a computer touch screen and is instructed to "chase" a moving tile around the grid. This is followed by the timed chase test, where they must chase the target for 30 sec. The subject is then shown the same 10 x 10 grid of tiles on a computer touch screen. A 28-step pathway is hidden among the 100 possible locations, with the start and finish locations in the top left and bottom right of the grid, respectively. The subject is instructed to move one step from the start location and to continue, one tile at a time, toward the end. The subject moves by touching a tile next to the current location with the stylus. After each move, the computer indicates whether it is correct or incorrect. If a choice is incorrect, the subject must touch the last correct location and then make a different tile choice to advance toward the end. While moving through the hidden maze, the subject is required to adhere to two rules: no diagonal moves or touching the same tile twice in succession and no moving backwards along the pathway. The subject learns the 28-step pathway though the maze on the basis of this trial and error feedback. Once completed, the subject is returned to the start location and repeats the task, usually 4 more times, trying to remember the pathway just completed. There are 20 well-matched alternate forms for this task, and these are selected in pseudo-random order to ensure that no subject completes the same hidden path until all 20 have been completed. The software measures the total number of errors.

Cognitive Bias Computer Tasks: It is documented that individuals with emotional or dependence disorders exhibit biased attention toward stimuli associated with their disorder. This bias appears to diminish following successful treatment. Several tasks will be administered: the dot-probe attention task, the primed attention task, the implicit association task, and a go/nogo inhibition task. Generally, subjects will be told

that the purpose of the task is to see how quickly and accurately they can detect targets presented on a display terminal. During the tasks, the subject will be seated in front of an eye level computer screen. Alcohol, nonalcohol, pleasant and unpleasant pictures will be presented on the screen. Subjects will be given specific instructions for each task and will be asked to respond appropriately by pressing a button.

Controlled Oral Word Association Test (COWA) is a verbal fluency test that takes approximately 5 minutes to administer and measures spontaneous production of words beginning with a designated letter [46]. This measure will be used to examine the effects of topiramate on verbal fluency.

Wechsler Adult Intelligence Scale-Third Edition Digit Span subtest [47] will be used to assess verbal working memory and explore the potential effects of topiramate on verbal working memory.

6.4 Weekly Visits (approximately 50 minutes)

At each weekly visit, subjects in both medication groups will receive medical management (MM) [33]. This provides a basic clinical intervention that was designed to be used in conjunction with prescribed medication, and to be easily implemented by medically trained practitioners in non-specialty settings. The treatment will support subjects' efforts to reduce their drinking.

The first session (conducted right after the first MRI scan) will consist of a review of the results of the initial evaluation, identifying any medical concerns. This session will also use the brochure *A Guide to Sensible Drinking*, developed for use in the World Health Organization Brief Intervention Study project. The subject is then provided with a rationale and information about pharmacotherapy and the importance of adherence. At each visit, assessment and counseling (lasting approximately 15 minutes) are conducted. During these sessions, the nurse will perform a medical check on the subject's general functioning, obtain vital signs and weight, ask about medication side effects and concurrent medications, monitor the subject's medication adherence, and as appropriate, make recommendations on strategies for medication adherence for the subject to follow until the next visit. Men will be advised to consume no more than 4 standard drinks per day and 12 standard drinks per week and women will be advised to consume no more than 3 drinks per day and 8 drinks per week. Because subjects will not be physically dependent on alcohol, reduction of heavy drinking is a safe and ethical goal. The research technician or coordinator will measure the subject's breath alcohol concentration, perform a brief assessment of the subject's drinking, review the self-administered BDI to assess suicidal thoughts/ideation (and discuss with the nurse and/or physician, if there is endorsement of suicidal thoughts). For patient safety during travel, subjects will be instructed not to drink prior to study visits. At each visit, the subject's BrAC, weight, and vital signs will be measured. Subjects must have a breath alcohol level of 0.00 g% to complete the screening visit, 2 lab MRI scan visits, and endpoint visit, and below 0.05 g% to complete the weekly study visits. Study staff will follow TRC standard operating procedures for all subjects that present with a breath alcohol level above 0.00 g% at study visits.

Throughout the study, if a subject misses a study visit due to a vacation or an unforeseen event, the study nurse will provide the subject with enough study medication to ensure that he or she will be able to maintain the daily dosage of study medication until the next scheduled visit. The nurse will also provide instructions on how to take the study medication as per the dosing schedule. Study nurses will instruct subjects to call the TRC at any time to discuss any problems or concerns they may have while taking the study medication. All subjects will be provided phone numbers to contact the study staff during office hours and the beeper number for off-hours contact 24 hours a day. Subjects will be asked to come in for their next study visit as soon as possible.

If a subject calls to cancel a scheduled study visit due to an unforeseen event, study personnel will reschedule the study visit for as soon thereafter as possible. Study staff will mail the study medication to the subject via registered mail under the supervision of a study nurse. Staff will mail the study medication with the intent to reach the subject, before he or she runs out of study medication. The subjects will only be provided with enough study medication to ensure that they will be able to maintain their daily dosage of study medication until their next scheduled visit. The nurse will provide instructions over the phone on how to take the study medication as per the dosing schedule and record any adverse events that have occurred since the last study visit. Study nurses will instruct subjects to call the TRC at any time to

discuss any problems or concerns they may have while taking the study medication. Study staff will make efforts to reschedule missed study visits as soon as possible. An investigator will determine how many additional weeks of study medication a subject will be allowed to receive without attending a study visit.

6.5 Laboratory/MRI Session 2 Visit (approximately 3.5 hours)

During week 7, subjects will complete the 2nd scanning session. Procedures for the Laboratory/MRI Session 2 visit are the same as the 1st Laboratory/MRI Session procedures.

Early Termination Visit:

All patients (including those who discontinue treatment prematurely) will be asked to complete an end-of-treatment evaluation and to complete all scheduled assessments to facilitate intention-to-treat (ITT) analyses. All patients will be informed of these procedures prior to study enrollment. Patients will be compensated $50 for completing the end-of-treatment visit. Patients who decide to terminate the study prior to week 8 will also receive $50 upon completion of the end-of-treatment procedures. For patients who withdraw early and do not wish to continue with study visits/procedures, all end-of-treatment procedures will be administered at the time of withdrawal. Such patients will also be asked to undergo in-person or telephone follow-up at end-of-treatment for collection of the remaining treatment-phase Timeline Follow-back data.

6.6 Endpoint Visit (approximately 2 hours)

Following study drug taper, subjects will complete the Endpoint visit. During this visit, subjects will complete: 1) a breathalyzer to ensure a BrAC of 0.00 g%, 2) a blood draw (GGTP only), 3) brief questionnaires (including BDI for suicidal ideation,, and Endpoint visit), 4) Cogstate battery, and 5) Medication Questionnaire. Subjects will be eligible to request and receive de-briefing after completing the Endpoint Visit. The procedure for debriefing subjects involves the following: (1) study staff informs subjects at the Endpoint Visit that they are eligible to learn from the pharmacy whether they received active medication or placebo during the study, (2) if the subject wishes to receive this information, study staff will provide UPENN IDS an envelope with postage and the subject's address, along with the "Pharmacy Debriefing" sheet, which notes the subject's name & ID#, (3) the pharmacy technician will mail the subject the appropriate letter indicating the medication assignment, (4) study staff will remain blinded to study medication assignment.

Schedule of Assessments

Instrument	**Visit 0 Screening**	**Visit 1 MRI**	**Visits 2-6**	**Visit 7 MRI**	**Visit 8**	**Visit 9 Endpoint**
Breath Alcohol Concentration & Vital signs	X	X	X	X	X	X
Study Overview & Informed Consent	X					
Medical History & Physical Exam	X					
Laboratory tests (Blood for CBC, GGTP, HIV and DNA)	X					X (GGTP only)
MRI video	X					
MRI safety sheet (metal)	X	X		X		
Urine pregnancy test	Females	Females		Females		
Urine drug toxic screen	X	X		X		
Blood sample (2 Tbsp)	Females	Females		Females		
Demographic interview	X					
Structured Clinical Interview for DSM	X					Alcohol Module Only
Wechsler Abbreviated Scale of Intelligence	X					
Timeline Follow-Back Interview	X	X(brief)	X(brief)	X(brief)	X(brief)	X(brief)
Beck Depression Inventory	X	X	X	X	X	X
Short Index of Problems	X			X		X

Fagerstrom Test of Nicotine Dependence	X					X
Obsessive Compulsive Drinking Scale	X	X		X		X
Alcohol Urge Questionnaire	X	X		X		X
Within Session Rating Scale		X		X		
Clinical Institute Withdrawal Assessment for Alcohol Scale	X	X		X		
CogBias Tasks		X		X		
Cogstate Battery		X		X		X
Controlled Oral Word Association test		X		X		
Digit Span		X		X		
Medical Management		X	X	X	X	X
Endpoint/ Termination Form						X
Medication Questionnaire						X
Measures of Treatment		X	X	X	X	X

7 Statistical Plan

7.1 Sample Size Determination

The current sample size is based on the need to pilot our alcohol and non-alcohol audio-visual videos both on- and off-magnet through computerized tasks and during pCASL perfusion fMRI scanning.

7.2 Statistical Methods

7.2.1 Imaging Data Processing

Prior to performing analyses, brain data are examined for gross movement and full image acquisition. A Statistical Parametric Mapping (SPM)-based ASL data processing toolbox is used for data analyses. ASL image pairs are realigned to the mean of all control images and spatially smoothed with a 3D isotropic Gaussian kernel with full width at half maximum of 10mm. CBF image series are generated using a simplified two-compartment model with the sinc interpolation method for CBF calculations. The mean control image of each subject's data is co-registered to a high-resolution 3D T1 structural image using the mutual information based co-registration algorithm provided by SPM8. The same co-registration parameters are used to co-register the CBF maps to the structural image. The structural image is then spatially normalized to the Montreal Neurological Institute (MNI) standard brain. The same parameters are used to normalize the CBF images to the MNI standard space. Each subject's normalized mean control images are segmented using SPM8. The segmented gray matter masks are averaged and the overlap of subject's gray matter is extracted. This final mask is used for calculating global CBF for each session.

7.2.2 Imaging Data Analyses

Global CBF time course will be included in the model as a covariate to examine the effects of topiramate on regional CBF. No temporal smoothing will be applied. Contrasts between conditions (alcohol cue vs non-alcohol cue; scan 1 vs scan 2) will be defined in the general linear model to assess the voxel by voxel CBF difference. Using the corresponding parametric maps of this contrast (β maps), random effects analysis will be employed to test for a significant main effect of condition with a statistical parametric map of the T statistic at each voxel for population inference for each session for the placebo and topiramate groups (second-level analysis). A 2x2 factorial design matrix will be used to assess the effects of the pharmacological manipulation by including the group (topiramate vs placebo) and condition (scan 1 vs scan 2) as the two factors. An associated contrast will be defined in this model to examine administration effects. This two-stage analysis is theoretically equivalent to a 2-way analysis of variance (ANOVA). Simple regression analyses will be conducted on CBF with the change in craving scores [post-alcohol cue minus pre-alcohol cue craving scores, number of heavy drinking days during the past 30 days, and age] as covariates of interest to test for prognostic brain/behavioral correlations. For the exploratory aim, subjects will be grouped by genotype (CC vs A-allele carrier) to examine the moderating effects of rs2832407 in

GRIK1 on topiramate effects using the same simple regression analyses described above. We will limit this analysis to European Americans, as that is the population in which the preliminary findings were obtained and allele frequencies differ significantly by population.

7.2.3 Behavioral Analyses

Statistical significance tests use an alpha of .05 unless otherwise noted. Continuous demographic variables (e.g., age, education, quantity/frequency of alcohol use) are checked for normality, transformed if necessary, and summarized by calculating means, standard deviations and ranges. Scores on each factor will be included as covariates of interest with respect to perfusion fMRI data and genetic variance. Analysis of variance will be used to assess demographic differences across groups. Nominal demographic variables (e.g., race, sex, genotype) are summarized by calculating proportions and compared across groups using chi square analyses. Demographic (age, years education, monthly income) and clinical (depression, anxiety) will also be summarized.

7.2.4 Genetic Analyses

Genotyping will be carried out by Dr. Joel Gelernter at Yale University. Blood will be coded and shipped to Dr. Joel Gelernter's lab at Yale University. Samples will be shipped without identifiers, on dry ice following University of Pennsylvania and international shipping procedures. Staff will send blood shipments in batches and verify that shipments arrived at the lab maintaining tracking logs of all samples sent. DNA will be purified from whole blood using the PureGene kit (GentraSystems, Minneapolis, MN). We typically obtain ~30mg of high-quality DNA per ml of blood extracted. TaqMan alleleic discrimination assays have been designed (for the SNPs already examined) or will be designed (for SNPs still to be examined, e.g., in *GRIK1*) using Primer Express 3.0 software (Applied Biosystems Inc.). Genotyping will be performed using the 5'-nuclease TaqMan closed-tube fluorescence method and an ABI 7500 Sequence Detector System for post-PCR plate reads.

7.3 Subject Population for Analysis

Protocol-compliant subjects' data will be used for analysis.

8 Safety and Adverse Events

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the

other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the laboratory/scan session (approximately 2 weeks from informed consent).

Pre-existing Condition
A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the IRB of any adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The IRB will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, an investigator or staff member must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

8.3.1 IRB Notification by Investigator

A Serious Adverse Event (SAE) must be reported to the IRB within 72 hours of the event. The investigator will keep a copy of this SAE form in the study binder.

At the time of the initial report, the following information will be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study participation was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study participation

Significant new information on ongoing serious adverse events should be provided promptly to the IRB.

8.4 Unblinding Procedures

In the event that subjects are prematurely discontinued, it will be necessary to avoid breaking the blind whenever possible, in order to protect the integrity of the study. If an emergency necessitates that the blind be broken, only the pharmacist will have access to the unblinding codes and will be given the names of the staff with authority to request that the blind be broken. If the IDS or hospital pharmacy is contacted by other persons in requesting the study blind be broken for a subject, and Drs. Wetherill and Kranzler are not reachable, the pharmacist will act according to his/her best judgment in deciding whether or not to break the study blind for that subject. The hospital pharmacist can be reached 24 hours a day by beeper to rapidly access subject unblinding codes.

The pharmacy emergency beeper number is: 215-555-1212.

8.5 Medical Monitoring

It is the responsibility of the physician investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 10 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6 Protection of Subjects

Complementing the safety measures noted above, additional procedures will be followed to protect the safety of the research subjects. Potential Subjects will be screened for medical illnesses that would preclude the use of topiramate. Subjects selected for the study will be evaluated weekly while receiving study drug treatments. AEs will be monitored weekly and a study physician will be available at all times to evaluate and treat adverse effects of the medication. On a weekly basis weights and vital signs will be obtained.

Significant AEs will result in exclusion from the study. Venipuncture will be carried out with good aseptic technique by an experienced phlebotomist, nurse, or physician. Venipuncture sites will be monitored carefully for signs of infection. At the conclusion of randomized medications, a physical examination, STUDY LABORATORY TESTS, and a urine pregnancy test (if female of childbearing capability) will be performed. Subjects will be given a 24-hour emergency number they can call if necessary. The PI or study psychiatrist will clinically follow all subjects who are discontinued due to a serious AEs until the AE resolves and becomes completely stable, unless a referral to another physician (i.e. specialist) is clinically indicated or requested by the subject.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Records, filed in the IRB office, verify that all research project personnel have completed training in the protection of human research subjects in accordance with the guidelines of the U.S. Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP). The study staff (PI, Clinical research coordinator, etc.) will keep all study medical records (including any codes to de-identified data) under lock and key in a secure location, as required by law. Only date and time of the research visit and lab specimen data will be placed in the client's existing electronic medical record. All electronic data and files (e.g., database, spreadsheet, etc.) containing identifiable subject information shall be password protected. Any computer hosting such files shall have a BIOS password to prevent access by un-authorized users. If subject data are to be exchanged with others, the data will be coded. If identification is necessary, then the data will be encrypted while en route to the recipient with strong encryption levels (≥ 128 bits for symmetric encryption (DES) and ≥ 1024 bits for asymmetric encryption (RSA).

All data and blood specimens will be stored without direct identifiable information, but will be identifiable via a linking code. The secured research records are labeled with code numbers only (names and other identifying information are kept separate from research records). Access to hard copy data is only given to staff members working on the study. Only staff members designated to handle or analyze study samples will have access to the samples and their storage. Coded blood samples are stored in clinic-specific refrigerators and freezers, which are located in secure rooms. As per routine in the CSA, all electronic files (e.g., database, spreadsheet) will be password protected. Any computer hosting such files will have a BIOS password to prevent access by un-authorized users.

Blood will be collected for DNA analysis. The information derived from analysis of the subjects' DNA will not be provided to the subject, since at the present time the existing preliminary genetic data for predicting response to topiramate do not provide a basis for genetic counseling. Should that situation change over the course of the study, procedures will be developed in conjunction with the UPenn IRB, to provide subjects with relevant information on genotype and to counsel them in relation to that information. While the study is open, DNA samples will be coded with a number that provides an indirect link to the subject's identity (samples will be accessible only by the researchers and staff involved with this study). Upon completion of the study, the sample will be kept in storage indefinitely. However, the sample will forever be separated from all identifiers. These de-identified samples may be shared with other researchers and used in other

projects. The lab procedures for storage include a passcode-protected locked room, and secure storage freezers. All samples will be retained securely as per lab protocols.

9.2 Source Documents

Source data is all information, original records, observations, or other activities during participation in the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the laboratories.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated.

9.4 Records Retention

It is the investigator’s responsibility to retain study essential documents for at least 3 years after the closure of the study with the IRB.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan described below. The Principal Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g., diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

The Principal Investigator and research staff will monitor the study. Written monitoring procedures for monitoring clinical investigations, proposed by the OHR and previously established at the CSA will be implemented to assure the quality of the study and to assure that each person involved in the monitoring process carries out his or her duties.

The Principal Investigator will maintain a record of the findings, conclusions, and action taken to correct errors noted by the monitor for each visit.

Monitoring Responsibilities: The monitor, in accordance with local and NIH requirements, should ensure that the study is conducted and documented properly by carrying out the following activities:

a. Verifying that the investigator has adequate qualification and resources and these remain adequate throughout the study period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the study and these remain adequate throughout the study period.
b. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
c. Verifying that written informed consent was obtained before each subject's participation in the study.
d. Verifying that the investigator is enrolling only eligible subjects.
e. Reporting the subject recruitment rate.
f. Verifying that source data/documents and other study records are accurate, complete, kept up to date, and maintained.

g. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated and identify the study.
h. Checking the accuracy and completeness of the CRF entries, source data/documents, and other study related records against each other.
i. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained, and initialed by the investigator or by a member of the study staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.
j. Determining whether all adverse events (AE's) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the applicable regulatory requirement(s).
k. Determining whether the investigator is maintaining the essential documents.
l. Communicating deviations from the protocol, SOP's, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.
m. Follow the University SOP's, GCP, and the applicable regulatory requirements.

Study Monitoring
The study Principal Investigator and research staff have prepared a case record form (CRF) that is designed to reduce coding errors and promote data quality. Each page of the CRF will contain a header that includes the title of the protocol, the protocol number, the subject randomization number, subject screening number, and visit number. The technicians are responsible for data entry. The research charts will be maintained separately from the CRF and will contain subject information that is not entered in the study CRF database.

Regulatory Binder: A detailed Regulatory Binder will be assembled. Any changes to procedures are documented in this section. This binder is the backbone of quality assurance. We use this binder to train any new study personnel and for reference so that our policies and procedures are standard throughout all phases of the protocol. The 'Measures' section of the binder addresses, specifically all forms and instruments that comprise the CRF. A Table of Contents has been prepared that contains all the forms used in the study.
The study manual will include

- study protocol research team names, titles, roles and responsibilities, work and home phone numbers
- purpose of study, study intent and rationale
- all study procedures for each team member (PIs, technicians, study coordinator, pharmacists, nurses, physicians, etc.)
- recruitment and screening procedures
- intake procedures
- study phase procedures
- completion/discontinuation procedures

Data Collection Training
The CSA provides comprehensive data collection training for all research technicians (RTs). RTs receive training on how to proceed with problematic subjects. RTs are extensively trained on all MRI procedures. RTs are trained to follow the general data collection guidelines listed below.

- RTs should be present when subject is completing instruments.
- Research interviews and evaluations should be administered in a private, quiet office or area.
- Instruments are introduced and explained the same way each time to each subject.
- Order of research assessments should be maintained, as much as possible.
- Order of specimens obtained should be maintained as much as possible.
- RTs should show an interested, polite, appropriate, and helpful demeanor.

Quality assurance (QA) procedures
Changes to the CRF and the study database are strictly monitored. After a single line is drawn through the corrected data point, the RT documents the change by placing his or her initials and the date of the change adjacent to the correction. Typical QA responsibilities of the RT include:

- Checking all data during or immediately after study visits.
- Checking charts at predetermined points during the study (initials and date of checker are required on each form checked).
- Performing the initial data check after a few charts have been entered.
- Performing a 10% data check when all data have been entered.

Typical responsibilities of the PI include:
- Monitoring and reporting on RT interviewing and data collection proficiency at subject study visits.
- Checking charts at predetermined points during the study (initials and date of PI are required on each form checked).
- Supervising study database checks.
- When databases, in Filemaker Pro or other applications, are developed by the research staff, only the data checked by the RT are entered. Data sets are double checked in pairs by technicians. The PI supervises any corrections to the data set and reviews the completed database before the information is used in any reports or analyses.
- The PI holds meetings with the RTs to report and review the project and data entry status.
- PI reviews lab results and screening information for potential subjects.
- PI reviews adverse events on at least a weekly basis.

Study Logs and Reports
Study logs are routinely maintained in order to keep computerized back up records of identifying and socio-demographic characteristics and experimental group status. The study subject log usually includes subjects' initials, study number, CRF number, date of birth, race, medication start dates, subject status (active, drop-out, completer, follow-up) and relevant dates and comments.

Data Storage on Site
The CRFs and research charts are stored in file rooms specifically designed for data storage. All study data are housed in locked file cabinets. Only designated members of the research team have access to the file cabinets containing research data. Data are kept on site for not less than three years after the subject has completed the final assessment. Data are then eligible for archiving.

10.2 Auditing and Inspection

The investigator will permit study-related monitoring, audits, and inspections by the IRB and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

11.1 Consent Procedures

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 (See Subject Informed Consent Form). This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

The investigator or designee will obtain informed consent before any study procedures occur, explaining all procedures in detail in an individual session. The consent form and explanation will include; detailed information about functional magnetic resonance imaging, the rationale for why it is being used, length of participation, as well as safeguards and emergency procedures. The collection of all lab specimens will be described in detail, as will the number and frequency of the research interviews and self-assessments. Subjects will be assured that their participation is voluntary and that withdrawal from the study would not jeopardize current or future participation in research studies. All subjects will be informed of potential risks and benefits involved in the study.

12 Study Finances

12.1 Funding Source

This study will be financed by the Department of Psychiatry.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan. All University of Pennsylvania investigators will follow the University conflict of interest policy.

12.3 Subject Stipends or Payments

Subjects will receive 2 SEPTA tokens (valued at $4.50) for travel for each scheduled appointment (all visits, even if subject does not pass the consent/screening), $75 for completing the initial laboratory/MRI session visit, $5 for returning medication bottles during weekly visits, $20 for completing Week 6 visit, $75 for completing the second MRI scan visit 7, and $25 for completing the Endpoint Visit. The total amount that subjects can receive for full participation in the research study is $235.00 plus 20 SEPTA tokens for a total of $280.00. Subjects who choose the double-booking option have the possibility of receiving $305.00, if the subject attends the scan session but is not scanned at double-booking appointment.

Table 3. Schedule for Study Payments

Visit	Payment	SEPTA tokens	Cost ($2.25/token)
Screening	$0	2 tokens	$4.50
Week 1 (Baseline & MRI 1)	$75	2 tokens	$4.50
Week 2	$5 returning med bottles	2 tokens	$4.50
Week 3	$5 returning med bottles	2 tokens	$4.50
Week 4	$5 returning med bottles	2 tokens	$4.50
Week 5	$5 returning med bottles	2 tokens	$4.50
Week 6	$20 + $5 returning med bottles	2 tokens	$4.50
Week 7 (MRI 2)	$75+5 returning med bottles	2 tokens	$4.50
Visit 8 (Taper started)	$5 returning med bottles	2 tokens	$4.50
Visit 9 (Endpoint)	$25 + $5 returning med bottles	2 tokens	$4.50
Totals	Up to $235	20 tokens	$45.00

*Subjects will receive a portion of the payment based on completion of study visit and returning both medication containers (i.e., $2.50 for returning only one of 2 bottles).

13 References

1. Alcoholism, N.I.o.A.A.a. *NIAAA recognizes alcohol awareness month*. 2013 [cited April 1, 2013 April 29, 2013]; Available from: http://www.niaaa.nih.gov/news-events/alcohol-awareness-month-2013.
2. Nelson, D.E., et al. Alcohol-attributable cancer deaths and years of potential life lost in the United States. American journal of public health 103:641-648, 2013.
3. Harris, A.H., et al. Pharmacotherapy of alcohol use disorders in the Veterans Health Administration. Psychiatric services 61:392-398, 2010.
4. Sinclair, J.D. Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. Alcohol and alcoholism 36:2-10, 2001.
5. Mason, B.J., et al. Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: the role of patient motivation. Journal of psychiatric research 40:383-393, 2006.
6. Oliva, E.M., et al. Barriers to use of pharmacotherapy for addiction disorders and how to overcome them. Current psychiatry reports 13:374-381, 2011.
7. Mark, T.L., H.R. Kranzler, and X. Song. Understanding US addiction physicians' low rate of naltrexone prescription. Drug and alcohol dependence 71:219-228, 2003.
8. Rosner, S., et al. Acamprosate for alcohol dependence. The Cochrane database of systematic reviews CD004332, 2010.
9. Franck, J. and N. Jayaram-Lindstrom. Pharmacotherapy for alcohol dependence: status of current treatments. Current opinion in neurobiology 23:692-699, 2013.
10. *VA/DOD Clinical Practice Guidelines for Management of Substance Use Disorder (SUD): Guideline Summary*. 2009, US Department of Veterans Affairs/Department of Defense: Washington DC.
11. Mark, T.L., et al. Physicians' opinions about medications to treat alcoholism. Addiction 98:617-626, 2003.
12. Hargreaves, G.A. and I.S. McGregor. Topiramate moderately reduces the motivation to consume alcohol and has a marked antidepressant effect in rats. Alcoholism, clinical and experimental research 31:1900-1907, 2007.
13. Breslin, F.J., B.A. Johnson, and W.J. Lynch. Effect of topiramate treatment on ethanol consumption in rats. Psychopharmacology 207:529-534, 2010.
14. Johnson, B.A., et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 361:1677-1685, 2003.
15. Johnson, B.A., et al. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA : the journal of the American Medical Association 298:1641-1651, 2007.
16. Miranda, R., Jr., et al. Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. Alcoholism, clinical and experimental research 32:489-497, 2008.
17. Rubio, G., et al. Effects of topiramate in the treatment of alcohol dependence. Pharmacopsychiatry 37:37-40, 2004.
18. Baltieri, D.A., et al. Comparing topiramate with naltrexone in the treatment of alcohol dependence. Addiction 103:2035-2044, 2008.
19. Florez, G., et al. Topiramate for the treatment of alcohol dependence: comparison with naltrexone. European addiction research 17:29-36, 2011.
20. Kenna, G.A., et al. Review of topiramate: an antiepileptic for the treatment of alcohol dependence. Current drug abuse reviews 2:135-142, 2009.
21. Childress, A.R., et al. Limbic activation during cue-induced cocaine craving. The American journal of psychiatry 156:11-18, 1999. 2820826
22. Langleben, D.D., et al. Acute effect of methadone maintenance dose on brain FMRI response to heroin-related cues. The American journal of psychiatry 165:390-394, 2008.
23. Franklin, T.R., et al. Limbic activation to cigarette smoking cues independent of nicotine withdrawal: a perfusion fMRI study. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 32:2301-2309, 2007.
24. Grusser, S.M., et al. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. Psychopharmacology 175:296-302, 2004.

25. Hutchison, K.E., et al. Olanzapine attenuates cue-elicited craving for tobacco. Psychopharmacology 175:407-413, 2004.
26. Goldman, M., et al. Reward-related brain response and craving correlates of marijuana cue exposure: a preliminary study in treatment-seeking marijuana-dependent subjects. Journal of addiction medicine 7:8-16, 2013. 3567235
27. Myrick, H., et al. Effect of naltrexone and ondansetron on alcohol cue-induced activation of the ventral striatum in alcohol-dependent people. Archives of general psychiatry 65:466-475, 2008. 2504413
28. Kranzler, H.R. and H.J. Edenberg. Pharmacogenetics of alcohol and alcohol dependence treatment. Current pharmaceutical design 16:2141-2148, 2010.
29. Kranzler, H.R., et al. Association of markers in the 3' region of the GluR5 kainate receptor subunit gene to alcohol dependence. Alcoholism, clinical and experimental research 33:925-930, 2009. 2772659
30. Del Re, A.C., et al. Prescription of topiramate to treat alcohol use disorders in the Veterans Health Administration. Addiction science & clinical practice 8:12, 2013. 3716908
31. Johnson, B.A. and N. Ait-Daoud. Topiramate in the new generation of drugs: efficacy in the treatment of alcoholic patients. Current pharmaceutical design 16:2103-2112, 2010. 3063512
32. Kranzler, H.R., et al. Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. Am J Psychiatry 171:445-452, 2014. 3997125
33. Pettinati, H.M., et al. Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence. COMBINE Monograph Series, Volume 2, DHHS Publication No. (NIH) 045289; Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism. . 2004.
34. Sanchez-Craig, M., D.A. Wilkinson, and R. Davila. Empirically based guidelines for moderate drinking: 1-year results from three studies with problem drinkers. American journal of public health 85:823-828, 1995. 1615483
35. Wechsler, D., *Wechsler Abbreviated Scale of Intelligence manual*. 1999, San Antonio: Harcourt Brace & Company.
36. Sobell, L.C. and M.B. Sobell, *Timeline Follow-back: A technique for assessing self-reported ethanol consumption*, in *Measuring Alcohol Consumption: Psychosocial and Biological Methods*, J. Allen and R.Z. Litten, Editors. 1992, Humana Press: Totowa, NJ. p. 41-72.
37. Miller, W.R. and J.S. Tonigan. The Drinker Inventory of Consequences (DrinC), NIAAA Project MATCH Monograph Series Vol. 4 NIH Publ. No. 95-3911, 1995. 1995.
38. Feinn, R., H. Tennen, and H.R. Kranzler. Psychometric properties of the short index of problems as a measure of recent alcohol-related problems. Alcoholism, clinical and experimental research 27:1436-1441, 2003.
39. Bohn, M.J., D.D. Krahn, and B.A. Staehler. Development and initial validation of a measure of drinking urges in abstinent alcoholics. Alcoholism, clinical and experimental research 19:600-606, 1995.
40. Fagerstrom, K.O. and N.G. Schneider. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. Journal of behavioral medicine 12:159-182, 1989.
41. Anton, R.F., D.H. Moak, and P.K. Latham. The obsessive compulsive drinking scale: A new method of assessing outcome in alcoholism treatment studies. Archives of general psychiatry 53:225-231, 1996.
42. Sullivan, J.T., et al. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). British journal of addiction 84:1353-1357, 1989.
43. Epperson, C.N., et al. Sex, GABA, and nicotine: the impact of smoking on cortical GABA levels across the menstrual cycle as measured with proton magnetic resonance spectroscopy. Biol Psychiatry 57:44-48, 2005. 4097033
44. Krejza, J., et al. Cerebrovascular reactivity across the menstrual cycle in young healthy women. Neuroradiol J 26:413-419, 2013.
45. Silveri, M.M., et al. Frontal lobe gamma-aminobutyric acid levels during adolescence: associations with impulsivity and response inhibition. Biol Psychiatry 74:296-304, 2013. 3695052
46. Ruff, R.M., et al. Benton Controlled Oral Word Association Test: reliability and updated norms. Arch Clin Neuropsychol 11:329-338, 1996.

47. Wechsler, D., *WAIS-III administration and scoring manual (3rd ed.)*. 1997, San Antonio, TX: The Psychological Corporation.

14 Appendix 1: Pilot Test Cue Sets (COMPLETED)

14.1 Background

The primary goal of this study is to elucidate the brain and behavioral mechanisms that mediate topiramate's reduction of heavy drinking, and one way that we propose to reach this goal is to examine the effects of topiramate on alcohol cue reactivity. As such, we need to ensure that our alcohol cues are effective in eliciting reward-related neural responses and that our non-alcohol cues do not. As part of Objective 1, we aim to pilot test our cue sets; therefore, this small substudy will acquire pilot data on up to 10 subjects to ensure that our cue sets are effective and will be useful for the study's other objectives.

14.2 Objective

Pilot test alcohol and non-alcohol cues in individuals with AUD to ensure brain and behavioral responses for remaining study objectives.

14.3 Design

Heavy drinkers who meet DSM-5 criteria for AUD will be recruited, screened, and consented, and if eligible will complete an MRI scan session. We will use perfusion fMRI during alcohol cue exposure to acquire brain and behavioral responses to alcohol and non-alcohol cues to pilot test the validity of our cue sets. Study duration for subjects is approximately one week and includes a consent visit and one scan session. Up to 10 individuals will complete the sub-study with the goal of obtaining 6 usable imaging data sets..

14.3.1 Primary Study Endpoints

The primary endpoints to be measured include:

- Self-report ratings of cues, subjective ratings of craving during/following cue exposure, and neuroimaging data on cerebral blood flow when the brain is at rest and when exposed to alcohol cues.

14.4 Subject Selection and Withdrawal

14.4.1 Inclusion Criteria

1) Physically healthy, as determined by a comprehensive medical history and approval of the study physician males or females who drink alcohol, ages 18-60.
2) Have an average weekly ethanol consumption of $\geq$24 standard drinks for men, or $\geq$18 standard drinks for women [34].
3) Females must be non-pregnant, non-lactating and either be of non-childbearing potential (i.e. sterilized via hysterectomy or bilateral tubal ligation or at least 2 years post-menopausal) or of child bearing potential but practicing a medically acceptable method of birth control. Examples of medically acceptable methods for this protocol include: the birth control pill, intrauterine device, injection of Depo-Provera, Norplant, contraceptive patch, contraceptive ring, double-barrier methods (such as condoms and diaphragm/spermicide), male partner sterilization, abstinence (and agreement to continue abstinence or to use an acceptable method of contraception, as listed above, should sexual activity commence), and tubal ligation.
4) Provide voluntary informed consent.

14.4.2 Exclusion Criteria

1) A current, clinically significant physical disease or abnormality on the basis of medical history.
2) History of head trauma or injury causing loss of consciousness, lasting more than five (5) minutes or associated with skull fracture or inter-cranial bleeding or abnormal MRI.
3) History of major DSM-IV Axis I diagnoses other than alcohol use disorder (except nicotine use disorder)
4) Presence of magnetically active irremovable prosthetics, plates, pins, permanent retainer, bullets, *etc*. (unless a radiologist confirms that it's presence is unproblematic). An x-ray may be obtained to determine eligibility given the possibility of a foreign body.
5) History of a serious psychiatric illness including psychosis, bipolar disorder, or suicidal or homicidal intent.
6) Claustrophobia or other medical condition preventing subject from lying in the MRI for approximately one (1) hour.
7) Current regular treatment with psychotropic medications (e.g., benzodiazepines, antidepressants), which affect neurotransmitter systems or a medication being used to treat alcohol use disorders (e.g., naltrexone, acamprosate).
8) Vision problems that cannot be corrected with glasses.
9) Body Mass Index (BMI) greater than or equal to 34, body girth greater than 52 inches and a head girth greater than 25 inches [Imaging data acquisition is impaired with high weight individuals].
10) Individuals suffering from or with a history of stroke and/or stroke related spasticity.
11) Individuals with a history of seizures.

14.5 Subject Recruitment and Screening

Subjects will be recruited from those who respond to IRB-approved advertisements. Advertisements will be in the form of IRB-approved radio ads, flyers, billboards, e-lists, and word of mouth. Individuals who have completed prior studies and meet study criteria will also be invited to participate if subject participation ended at least 30 days before the current study starts (i.e., no pharmacotherapy or psychotherapy for 30 days). An initial telephone interview covering recent medical status, substance use, treatment history, medication, and general psychiatric history will be conducted. The potential subject will be provided with an overview of the study and will be informed that all information obtained will be used to determine his/her eligibility for study participation. If the individual satisfies preliminary criteria and shows continued interest in participating in the study, an appointment will be made for further screening and the CSA. The screening process will be described, and the individual will also be informed that s/he must be available for at least two separate appointments during the screening week (unless the two appointment are combined). For details on Screening, see 14.7.2 Informed Consent and Screening Visit below.

14.6 Early Withdrawal of Subjects

14.6.1 When and How to Withdraw Subjects

Subjects with severe psychological symptoms (e.g., suicidal thoughts), those who fail to adhere to protocol requirements, and those withdraw consent will be withdrawn from the study and if applicable, referred for appropriate clinical care. If a subject is found to be pregnant during the study, she will immediately be withdrawn from the study, referred for obstetric evaluation, and advised to discontinue all drinking.

14.6.2 Data Collection and Follow-up for Withdrawn Subjects

We will make a strong effort (via phone calls and alternative contact information) to obtain follow-up information on all subjects who are prematurely withdrawn from the project.

14.7 Study Procedures

14.7.1 Initial Telephone Screen (approximately 20 minutes)

Subjects will be recruited from the Center for Studies of Addiction at 3900 Chestnut St. through local advertisements. Individuals who have completed prior studies or expressed interest in other research studies at the CSA, but were deemed ineligible due to AUD (e.g., nicotine studies), and meet study criteria will also be invited to participate if subject participation ended at least 30 days before the current study starts (i.e., no pharmacotherapy or psychotherapy for 30 days). Subjects who express interest are contacted by phone and participate in a telephone screening interview. The nature of the study, including the number of visits to the center and a description of fMRI procedures, subject protections and confidentiality, are described. If the caller is still interested, questions on general health are asked. If the applicant is determined to be eligible based on this screening, s/he is asked whether they accept or decline to participate. If the caller is still interested, s/he will be scheduled for an initial consenting appointment.

14.7.2 Informed Consent and Screening Visit (approximately 2 hours)

Upon arriving to the Informed Consent and Screening Visit, subjects will be asked to show legal identification and to complete a breathalyzer test to ensure a breath alcohol concentration (BrAC) of 0.000. Reading ability will be evaluated followed by a review of HIPAA privacy laws and the informed consent. Specifically, subjects will be provided a standard HIPAA form that contains privacy laws, and a study staff member will review the consent form with the subject, including an explanation of the study protocol, its risks, and potential benefits. Following resolution of any questions, subjects who appear to understand the nature of the study and consent will be asked to sign the study consent form. An entire copy of the informed consent form will be given to each subject. S/he is also reminded that the consent expresses willingness to participate but that the subsequent screening process will determine final eligibility. Further, s/he is reminded that participation is voluntary, and at any time, s/he may withdraw from the study.

Following consent, subjects will watch an fMRI video that simulates the experience of undergoing an MRI, and meet with the study nurse to complete a medical history, urine toxicology, and females will complete a urine pregnancy test. Subjects will also meet with study staff to complete additional assessments.

Measures obtained:

a. *Sociodemographic/subject information:* General demographic information, marital status, educational, and occupational information will be obtained.

b. The **Alcohol Urge Questionnaire (AUQ)** [39] is an 8-item, self-administered state measure assessing the urge for an alcoholic drink at the time the questionnaire is completed and provides an index of acute craving. The AUQ contains four items pertaining to the desire for a drink: two items regarding expectations of positive effects from drinking, and two items relating to the inability to avoid drinking if alcohol were present. This measure has strong correlations with measures of alcohol dependence and severity.

c. The **Timeline Follow-back (TLFB)** [36] will be used to estimate past 30-day drinking. 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. We will also measure tobacco and other substance use patterns using the TLFB.

d. **Structured Clinical Interview for DSM (SCID)** will be administered to obtain DSM-5 diagnosis of alcohol use disorder and, using DSM-IV criteria, to rule out other psychiatric disorders (except nicotine dependence).

14.7.3 Laboratory/MRI Visit (approximately 2 hours)

Interested, eligible, consented subjects will attend a laboratory/MRI session visit. During this visit, subjects will complete: 1) a breathalyzer to ensure a BrAC of 0.000, 2) a urine pregnancy test, 3) urine toxicology, 4) an MRI scan, and 5) brief questionnaires.

Prior to MRI scanning, subjects will meet with study staff who will prepare the subject for the MRI session. Subjects will also be asked to drink to satiety prior to starting the scan session to avoid potential confounding

effects of thirst on neural responses to cues. During the scanning session, subjects will be asked to lie still with their eyes open for a 5 minute resting baseline scan, followed by two 10-minute audio-visual clips consisting of either alcohol-related cues: individuals differing in race, age and sex who are drinking alcohol and using explicit language designed to induce appetitive desire for alcohol; or non-alcohol-related cues that are similar in content, but individuals relate interesting short stories that do not portray alcohol consumption or alcohol reminders. Subjects will also be asked their level of alcohol craving (on a scale from 0-10) before and after each audio-video clip. For MRI acquisition details, see 6.3 Study Procedures above.

Table 4. Schedule of Assessments for Pilot

Instrument	Visit 0 (Screening)	Visit 1 (MRI Scan)
Breath Alcohol Concentration	X	X
Study Overview & Informed Consent	X	
Medical History	X	
MRI video	X	
Urine toxicology	X	X
Urine female pregnancy test	X	X
Demographic interview	X	
Structured Clinical Interview for DSM	X	
Timeline Follow-Back Interview	X	
Alcohol Urge Questionnaire	X	X
Within Session Rating Scale		X

14.8 Statistical Plan

14.8.1 Sample Size Determination

The current sample size is based on the need to pilot our alcohol and non-alcohol audio-visual videos both on- and off-magnet through computerized tasks and during pCASL perfusion fMRI scanning.

14.9 Statistical Methods

14.9.1 Imaging Data Processing

Prior to performing analyses, brain data are examined for gross movement and full image acquisition. A Statistical Parametric Mapping (SPM)-based ASL data processing toolbox is used for data analyses. ASL image pairs are realigned to the mean of all control images and spatially smoothed with a 3D isotropic Gaussian kernel with full width at half maximum of 10mm. CBF image series are generated using a simplified two-compartment model with the sinc interpolation method for CBF calculations. The mean control image of each subject's data is co-registered to a high-resolution 3D T1 structural image using the mutual information based co-registration algorithm provided by SPM8. The same co-registration parameters are used to co-register the CBF maps to the structural image. The structural image is then spatially normalized to the Montreal Neurological Institute (MNI) standard brain. The same parameters are used to normalize the CBF images to the MNI standard space. Each subject's normalized mean control images are segmented using SPM8. The segmented gray matter masks are averaged and the overlap of subject's gray matter is extracted. This final mask is used for calculating global CBF for each session.

14.9.2 Imaging Data Analyses

Global CBF time course will be included in the model as a covariate to examine regional CBF. No temporal smoothing will be applied. Contrasts between conditions (alcohol cue vs non-alcohol cue) will be defined in the general linear model to assess the voxel by voxel CBF difference. Using the corresponding parametric maps of this contrast (β maps), random effects analysis will be employed to test for a significant main effect of condition with a statistical parametric map of the T statistic at each voxel for population inference. Simple regression analyses will be conducted on CBF with the change in craving scores [post-alcohol cue minus pre-alcohol cue craving scores] as covariates of interest to test for prognostic brain/behavioral correlations.

14.9.3 Behavioral Analyses

Statistical significance tests use an alpha of .05 unless otherwise noted. Continuous demographic variables (e.g., age, education, quantity/frequency of alcohol use) are checked for normality, transformed if necessary, and summarized by calculating means, standard deviations and ranges. Scores on each factor will be included as covariates of interest with respect to perfusion fMRI data.

14.10 Subject Stipends or Payments

Subjects will receive 2 SEPTA tokens (value of $4.50) and $10.00 for completing the screening visit with a negative urine toxicology screen. If the subject has a positive urine drug screen, they will be excluded from the study and only receive 2 SEPTA tokens for transportation to and from the TRC. Subjects will receive $75 for completing the MRI visit of this pilot substudy. The total amount that subjects can receive for full participation in the research study is $85.00 plus 2 SEPTA tokens for a total of $89.50.

***All remaining aspects of the substudy are described in Sections 8-13 above.**