N-ACETYLCYSTEINE TREATMENT OF ALCOHOL USE DISORDER IN VETERANS WITH TBI

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I. SYNOPSIS

The goal of the project is to improve the care of veterans with mild traumatic brain injury (TBI) and alcohol use disorder (AUD). The PI and coinvestigator are conducting a pilot controlled clinical trial to assess the efficacy of N-acetylcysteine (NAC) to reduce alcohol use and improve brain injury symptoms in veterans with TBI who have AUD. This proposed project builds upon our current IMN-funded research on topiramate pharmacotherapy for unhealthy alcohol use in veterans with TBI.

Exposure to injuries and stresses of combat is known to be associated with risk for both traumatic brain injury and hazardous and harmful alcohol use. Veterans, especially those involved in the Iraq and Afghanistan conflicts (Operation Iraqi Freedom [OEF], Operation Enduring Freedom [OEF] and Operation New Dawn [OND] have high rates of TBI. Because of the adverse interaction of heavy alcohol use and TBI, there is a clinical need for effective treatments to reduce hazardous and harmful alcohol use in these veterans. The proposed project directly builds on the PI's current pilot controlled trial of topiramate in veterans with PTSD and alcohol dependence. Acetylcysteine (NAC) has been shown to be efficacious in the treatment of dependence and may also have benefit in the treatment of PTSD, which often accompanies TBI.

Over 2 million veterans have served in the Iraq and Afghanistan conflicts -- Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) and 23%-30% may have sustained mTBI[1-3]. The prevalence of alcohol and other substance use disorders in OIF/OEF veterans with TBI is approximately twice that of veterans without TBI[1,4]. Although the majority of alcohol treatment studies have focused on AUD, the spectrum of unhealthy alcohol use includes both *hazardous* as well as *harmful* drinking. *Hazardous alcohol use* has been defined as drinking that exceeds recommended limits (≥14 drinks/week for men or 7 drinks/week for women or anyone over age 65) and is associated with higher prevalence of a wide range of medical and psychiatric morbidities. *Harmful alcohol use* is drinking that meets DSM-5 criteria for a diagnosis of AUD. Hazardous and harmful alcohol use (HHAU) is common among veterans; recent large epidemiologic studies found that 22-40% of OEF/OIF veterans screened positive for HHAU[5,6].

Neurocognitive impairment may be both an important contributor to, as well as a result of, alcohol use and TBI. AUD is associated with, or causal to, a wide variety of neurobehavioral harms. These include impulsivity, risk-taking behavior, irritability/mood instability, depression, and suicide risk. HHAU is also associated with deficits in executive functioning, learning, memory, and decision making, with increased impulsivity and risk-taking. Both HHAU's and TBI's association with impairments in self-control and decision-making are linked to ventromedial and orbitofrontal cortex dysfunction. Thus, both TBI and HHAU may independently and additively alter cognitive, emotional, and behavioral functioning. These alcohol- and TBI-related impairments can also synergistically increase the potential for risk-taking and contribute to many of the harmful behaviors seen in veterans with HHAU and TBI. By extension, they also affect their families, and the community at large.

NAC has been proposed as a neuroprotective agent that may benefit TBI, mediated through antioxidant and anti-inflammatory effects[7] and it may assist in reducing alcohol use. Reducing alcohol use and improving brain injury symptoms via NAC treatment may have the potential to improve cognitive functioning and reduce risky behavior in veterans with TBI. Reducing impulsivity and risk-taking propensity can be expected to reduce harmful behaviors that are tied to poor adherence to medical care, marital relationship problems, domestic and other forms of violence, and suicide. If, as expected, NAC treatment improves the management of TBI and AUD, it would have unambiguous benefits both for active duty military personnel and veterans.

Improving the care of veterans with TBI and unhealthy alcohol use is likely to help families and communities affected by the sequelae of these problems. Moreover, treatments that help veterans with TBI and unhealthy alcohol use are likely to be applicable to the general population of individuals with these comorbid problems.

The objectives of the study are: (a) to successfully recruit 30 veterans with mild TBI and hazardous or harmful alcohol use; (b) to test primary and exploratory hypotheses as described below.

Outcomes, products and deliverables: *Outcomes:* The primary treatment outcome will be percent heavy drinking days of alcohol per week. The secondary outcome will be TBI symptom severity as measured by the Neurobehavioral Symptom Inventory (NSI). The exploratory outcomes will be levels of executive functioning (impulsivity, risk-taking, and decision making) and other neurocognitive domains assessed over the course of the study. *Products:* Data will be collected on 8 weeks of treatment plus week 12 follow-up. *Deliverables:*

Interim and final poster presentations at Research Society on Alcoholism (RSA); Final report as a manuscript submitted for publication to a peer-review alcohol/addiction scientific journal.

This study is being sponsored by the Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC).

II. RESEARCH PLAN

A. GOALS AND SPECIFIC AIMS

The overall goal of the project is to improve the care of veterans with traumatic brain injury and unhealthy alcohol use. We will conduct a pilot controlled clinical trial to assess the efficacy of N-acetylcysteine (NAC) to reduce alcohol use and improve brain injury symptoms in veterans with TBI who consume alcohol at *hazardous or harmful* levels. This project builds upon our current ITN-funded research on topiramate pharmacotherapy for unhealthy alcohol use in veterans with TBI.

A.1. PRIMARY AIMS:

Aims:

Measure both alcohol use and TBI symptom severity over the course of the 12-week study in order to detect differential efficacy of NAC and placebo. Alcohol use treatment outcome will be the Percent Days of Heavy Drinking (PHDD) of alcohol

A heavy drinking day is defined using NIAAA (2007) criteria: any day with 5 or more drinks per day for men or 4 or more drinks per day for women[8]. The choice of PHDD as the primary outcome is based on its endorsement by a recent NIAAA consensus conference[9] and its increasing use in clinical trials [10-12]. TBI symptom severity will be measured with the Neurobehavioral Symptoms Inventory (NSI)[13,14] a measure of postconcussive symptom severity.

Hypotheses:

Our **two primary** aims examine group differences, to detect differential efficacy of NAC vs placebo (*between-group analyses*). We will test the following hypotheses with between-groups analyses:

1. NAC treatment combined with Medical Management (MM) alcohol counseling will have greater efficacy than placebo in reducing **percent heavy drinking days (PHDD).** A heavy drinking day is defined using NIAAA (2007) criteria: any day with ≥5 drinks for men or ≥4 for women[8]. PHDD as primary outcome is based on recent NIAAA consensus[9] and increasing use in clinical trials[10-12].

2. NAC treatment will have a greater efficacy than placebo in reducing TBI related symptoms. TBI symptom severity will be measured by the Neurobehavioral Symptom Inventory (NSI)[13,14].

A.2. EXPLORATORY AIMS:

Exploratory Aims:

Other exploratory aims will include obtaining additional measures of alcohol use, executive functioning (e.g., impulsivity and risk taking) and other domains of neurocognition, and examining the potential moderating effect of rs6465084 on NAC treatment response

Hypotheses:

NAC treatment will have greater efficacy than placebo in: a) reducing other alcohol use measures (percent drinking days per week, drinks/week, drinks/drinking day, alcohol craving, biomarkers); b) improving neurocognition. We will examine neurocognitive domains which include executive functioning (impulsivity, risk-taking, decision making), auditory-verbal learning and memory, verbal fluency, processing speed and working memory. We will also explore the potential moderating effect of rs6465084 on NAC treatment response.

A.3. FUTURE PLANS

If the results of this pilot NAC HHAU/TBI project are positive, the investigators will seek funding for a larger controlled trial through the Department of Defense CDMRP and related funding programs and/or NIAAA R01 mechanisms. We believe that we can derive a reliable estimate of effect size for planning a randomized controlled trial from this small parallel groups controlled pilot study. It will be useful to obtain estimates of

variability for the key outcome variables in this population of comorbid patients in order to inform future controlled trials. Furthermore, we would seek to partner with other investigators in future studies to include neuroimaging to examine potential pre to post treatment neurobiological changes which may occur with NAC treatment.

B. BACKGROUND AND SIGNIFICANCE

B.1. OVERVIEW

To achieve these aims, we will conduct a pilot prospective, parallel groups, randomized, double-blind, placebo-controlled flexible-dose clinical trial of NAC in 30 veterans with TBI and hazardous or harmful alcohol use. The 8-week treatment phase will consists of treatment with NAC or placebo, plus weekly manualized alcohol counseling, added to whatever usual TBI treatment participants may be receiving, including medication (exceptions being any alcohol treatment medications). The manualized counseling for alcohol use disorders will consist of Medical Management[15], an NIAAA manual-driven, low-intensity supportive program to promote adherence to the medication regimen and retention. Participants will continue to receive usual care for TBI and other medical and/or psychiatric disorders from their primary medical and mental health treatment providers. Participants will meet with research staff weekly to receive medication, counseling, and research assessments during the 8 weeks of study treatment. Participants will also be assessed at the week-12 follow-up visit.

B.2. THE CO-OCCURRENCE OF TBI AND HAZARDOUS AND HARMFUL ALCOHOL USE AMONG VETERANS

Over 2 million veterans have served in the Iraq and Afghanistan conflicts -- Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) and 23%-30% may have sustained traumatic brain injury (TBI)[1-3]. Evidence indicates that the prevalence of alcohol and other substance use disorders in OIF/OEF veterans with TBI is approximately twice that of veterans without TBI[1,4,16,17]. Post TBI, more service members have diagnoses of alcohol/substance abuse than any other selected condition except headache[18]. Evidence suggests that TBI may play a causal role in this relationship. For example, in a recent study, airmen with TBI were shown to have an increased risk for addiction-related disorders compared with a similarly injured non-*TBI* comparison group. The hazards for alcohol dependence and nondependent abuse of drugs or alcohol were significantly elevated in those with TBI as compared to controls[1].

B.3. UNHEALTHY ALCOHOL USE: HAZARDOUS AND HARMFUL ALCOHOL USE

Although the majority of alcohol treatment studies have focused on alcohol use disorder (AUD), the spectrum of unhealthy alcohol use includes *hazardous* as well as *harmful* drinking. *Hazardous* alcohol use has been defined as drinking that exceeds recommended limits (≥14 drinks/week for men or 7 drinks/week for women or anyone over age 69)[8,19] and is associated with higher prevalence of a wide range of medical and psychiatric morbidities[8]. *Harmful* alcohol use is alcohol use that meets DSM-5 criteria for a diagnosis of AUD[20]. Hazardous and harmful alcohol use (HHAU) is common among veterans; recent large epidemiologic studies found that 22-40% of OEF/OIF veterans screened positive for HHAU[5,6].

B.4. NEUROBEHAVIORAL INTERACTIONS OF HEAVY ALCOHOL USE AND TBI

Both TBI and HHAU are associated with impulsivity and impaired decision-making and linked to ventromedial and orbitofrontal cortex dysfunction[21]. Both TBI and HHAU are also associated with, or causal to, a wide variety of neurobehavioral harms. These include impulsivity, irritability/mood instability, depression, and suicide risk. Other impairment occur in attention, concentration, visual-spatial memory, and executive functioning -- including decision-making, risk-benefit analysis, and behavioral inhibition[22]. TBI and HHAU can synergistically increase the potential for these cognitive, emotional, and behavioral impairments and thereby increase risk-taking behavior.

Neurocognitive functioning has been shown to be an important moderator of substance abuse treatment outcome[21,23]. Neurocognitive impairment may therefore be both an important contributor to, as well as a result of, continued alcohol use in TBI. However, cognitive functioning has been shown to improve even after brief periods of abstinence from alcohol[21]. Reducing alcohol use may thus have the potential to improve cognitive functioning, improve decision-making and reduce risk-taking behavior in veterans with TBI.

B.5. LIMITS OF CURRENT PHARMACOTHERAPIES FOR AUD AND FOR HHAU IN TBI

Although there are several FDA-approved medications for the treatment of AUD, no consensus exits regarding medications to reduce *hazardous* alcohol use, and there are no published reports of pharmacotherapies for either AUD or other forms of HHAU *in patients with TBI*. Disulfiram, acamprosate, as well as oral and extended-release injectable forms of naltrexone are approved by the Food and Drug Administration (FDA) for the treatment of AUD. Topiramate is also an efficacious medication although not FDA-approved for AUD. However, these medications have limitations and at best show only modest to moderate efficacy[24]. The most rigorous controlled trial of disulfiram showed only questionable efficacy[25] and disulfiram treatment requires abstinence from alcohol. Naltrexone studies have generally supported its efficacy reducing drinking, although effect sizes are modest[24]. Naltrexone's opioid antagonism precludes its use in patients who require opioid analgesic treatment, a salient issue for many injured veterans with chronic pain conditions. Acamprosate has been found to reduce alcohol relapse rates in European studies[26], however, trials conducted in the United States, e.g. the COMBINE[27] study, have failed to establish its efficacy in intent-to-treat analyses. Disulfiram and oral naltrexone also have hepatotoxic potential, although low. The available treatments also have other clinically significant adverse effect burdens. Topiramate treatment, for example, as demonstrated by the PI's previous research (see below) is associated with cognitive impairment in veterans with AUD, a problem of particular relevance to individuals with TBI. Other difficulties with these medications are cost, with acamprosate and injectable naltrexone being the most costly. There is therefore a need to find novel alternative, safe, well-tolerated, and low-cost medications for the treatment of AUD, and in particular, for the treatment of HHAU in veterans with TBI.

C. PRELIMINARY STUDIES

C.1. N-ACETYLCYSTEINE BACKGROUND AND EVIDENCE FOR USE IN DISORDERS OR ADDICTION

N-Acetylcysteine (NAC) is FDA-approved, most commonly used as a mucolytic[28] and in the treatment of acetaminophen overdose[29]. NAC's potential as a treatment for substance use disorders is related to its roles in oxidative homeostasis and glutamate activity[30]. NAC is the acetylated precursor of the amino acid L-cysteine, and although it has a relatively low bioavailability (below 5%), NAC associated redox exchange reactions produce cysteine, which can cross the epithelial cell membrane and blood brain barrier in abundance[31]. Cysteine is involved in the synthesis of glutathione (GSH), a tripeptide composed of glutamate, cysteine and glycine, which serves as a ubiquitous antioxidant neutralizing oxidative free radicals[32]. NAC-derived cysteine also assists in the regulation of Glu through the cystine-Glu antiporter[30]. NAC increases activity of the catalytic subunit of the cysteine-Glu exchanger and Glu transporter 1 (GLT1)[33-35]. Through this system, glial astrocytes exchange cysteine for Glu, which is released into the extracellular space inducing an increase in the glutamatergic tone on presynaptic metabotropic Glu receptors 2/3 (mGluR2/3)[36], which in turn has an inhibitory effect on presynaptic glutamate release[36]. Both *acute* and *chronic* alcohol consumption has been shown to increase extracellular levels of glutamate in the nucleus accumbens (NAcc)[37,38]. Extracellular Glu in the NAcc is associated with cue-induced reinstatement of alcohol-seeking behavior[39]. The alcohol-induced dysregulation of extracellular Glu is likely due to an alteration in the mechanism of relase and reuptake of Glu similar to that shown in cocaine addiction[40-45]. With repeated exposure to cocaine, extracellular Glu is reduced in the NAcc via decreased tonic activation of relase-regulating mGlu2/3[38,41,46-48]. Modulation mGluR2/3 cysteine-Glu exchange via NAC restores basal extracellular levels of Glu and prevents cocaine[40,49,50] and heroin[51,52] seeking. More importantly, *reduction in glutamatergic transmission via activation of mGlu2/3 attenuates alcohol seeking behavior*[53,54]. In sum, NAC may regulate elevated extracellular glutamate[36] resulting from acute and chronic alcohol exposure[55], thus repairing faulty communication between NAcc and prefrontal cortex[56].

Medications that modulate the effects of Glu in the midbrain have shown clinical effectiveness in the treatment of AUD[57-59]. Additionally, animal models have demonstrated the ability of GSH to potentiate N-methyl-D-aspartate receptor response to Glu[30]. NAC can aid in the synthesis of GSH and it also simultaneously modulates dopamine (DA) transmission and DA-associated reactive oxygen species[60]. Medications that modulate Glu may suppress conditioned cue responses to alcohol after short-term abstinence[61], reduce aversive effects of alcohol withdrawal related to increased Glu and decreased central DA levels, particularly in the nucleus accumbens[62,63], and inhibit neuronal hyperexcitability[64] following withdrawal[65,66]. Moreover, NAC's

anti-inflammatory effects have also been implicated as playing a role in its potential therapeutic effects on the pathophysiology of substance use disorders[67].

NAC has been shown to have possible efficacy in the treatment of cocaine[68-70], cannabis[71,72] and nicotine dependence[73], pathological gambling[74], and in other psychiatric disorders marked by impulsivity/compulsivity[30,75-78]. There have been four open label[68,70,71,74] and six double-blind placebo-controlled randomized clinical trials (RCTs)[33,36,37,43-45] of NAC for addiction treatment. In an 8-week RCT for cocaine dependence, 111 participants were assigned to receive 1200 or 2400 mg of NAC or placebo per day[79]. Participants assigned to 2400 mg of NAC took longer to relapse and had less craving compared to placebo. Two smaller (n=13/15) cocaine RCTs showed NAC to inhibit cocaine cue reactivity more than placebo[69] and to reduce self-reported cocaine use, withdrawal symptoms, and craving[80]. An open study in 23 treatment seeking cocaine dependent individuals (26% with comorbid alcohol dependence) showed trends towards reductions in money spent and number of days of cocaine use[68]. In a four-week open-label trial of NAC in 24 treatment-seeking cannabis dependent individuals, NAC was associated with decreased self-reported cannabis use and craving [71]. Gray (2012)[72] confirmed these findings in an RCT of NAC in 116 cannabis-dependent adolescents. In a four-week RCT in treatment-seeking nicotine dependent participants, NAC reduced the number of cigarettes smoked[73]. Of relevance to this application's primary aims, Knackstedt et al.,[73] reported that the daily number of cigarettes smoked strongly covaried with alcohol use, which suggests a reduction in alcohol use in the sample of alcohol users in that study. Finally, a six-week RCT of NAC in 13 pathological gamblers, 83% showed decreased OCS compared to only 28% of participants receiving placebo[74]. Finally, in an ongoing IMN-funded pilot project (PI Kalivas), NAC appears to be efficacious in reducing alcohol and cocaine craving in individuals with PTSD and substance use disorder[81].

Taken together, these findings suggest NAC has utility in controlling reward-driven behavior in addictive disorders, potentially moderated through the glutamate system[82]. Additionally, in all of the mentioned studies, NAC was well tolerated, with only minor side effects. Of note, NAC, in combination with high-dose naltrexone, is being tested in an ongoing trial for the treatment of alcohol dependence (Gihyun Yoon; NCT01214083).

C.2. N-ACETYLCYSTEINE EVIDENCE FOR USE IN BRAIN INJURY SYMPTOM TREATMENT

NAC has been proposed as a neuroprotective agent that may benefit TBI. In TBI, a concussive force is imparted to the head from contact with an object or -- as is common among Iraq /Afghanistan veterans – a rapidly expanding pressure wave[83]. Injuries lead to dysfunction of the pulmonary and circulatory systems, with autonomic nervous system and neuroendocrine-immune system acitivation contributing to cellular brain injury[84]. The neuroprotective effects of NAC on TBI have been proposed to be mediated through antioxidant and anti-inflammatory effects[7]. In an RCT in 81 active duty service members with acute mTBI, NAC treatment resulted in improved cognitive test performance, reduced number of mTBI symptoms, and higher rates of complete symptom resolution after seven days of NAC treatment compared to controls[7]. Although this study was limited to acute mTBI, the authors suggest NAC treatment may be useful in other TBI settings.

In animal models, NAC has been shown to attenuate cellular injuries including oxidative stress[84-87], axonal injury[88,89], inflammation[90,91], apoptosis[92] and neurodegeneration[93,94]. Rodent models suggest NAC acts as an anti-inflammatory agent[87,90] and may aid in reducing TBI related behavioral deficits[91]. NAC (combined with minocycline) has been shown to attenuate myelin loss and modulate neuroinflammation, thus improving spatial learning, memory and set-shifting in mildly brain injured rats[91,95]. Chen et. al.[90], demonstrated NAC attenuation of TBI-induced proinflammatory response. In addition to neuroinflammation and oxidative stress, increased synaptic release of glutamate is also characteristic of TBI[96-99]. Yi et. al.,[94] demonstrated the effects of NAC to regulate both excitatory and inhibitory neurotransmission following TBI in rats. Similarly, Xiong et. al.[100], demonstrated NAC's ability to regulate GSH (glutamate regulator) in rat brain tissue in acute TBI. Taken together, NAC may be beneficial for the neuroprotective effects demonstrated in human and animal TBI studies in addition to its potential benefits in glutamatergic regulation.

C.3. N-ACETYLCYSTEINE EVIDENCE FOR COGNITIVE ENHANCEMENT

In AUD, deficits in executive functioning, learning, memory, and measures of decision making, impulsivity, risk-taking are well documented[101]. The neural circuitry in the prefrontal cortex plays an important role in inhibitory control[102,103], thus making it a target for therapeutic intervention[104]. NAC's ability to regulate

glutamate along with glutamate's critical role in synaptic plasticity and corresponding learning and memory[105] make it a promising therapeutic candidate. NAC has been shown to improve learning, memory and set shifting in animals[91,95], and is proposed as a potential treatment for dementia-related cognitive decline in humans[106]. Parachikova et al.,[107] demonstrated that NAC (and other supplements) improved cognition and decreased Alzheimer's neuropathology in mice. Increased cognitive functioning is beneficial in addiction treatment because it predicts greater motivation to change and better self-regulation of drinking behavior[21].

The combined evidence of NAC associated anti-oxidant[84], anti-inflammatory[7], glutamatergic[108] and related cognitive-enhancing benefits[104], tolerability[7,82,109], and capacity to prevent hepatic injury[29] provides support for a pilot trial of NAC treatment in veterans with TBI who are consuming alcohol at hazardous or harmful levels.

C.4. GENETIC MODERATION OF ALCOHOL PHARMACOTHERAPY RESPONSE

Until now, as with most psychiatric disorders, it has been difficult to predict which AUD patients will respond to which medication. Recently, evidence has emerged showing genetic moderating effects on AUD medication response. For example, topiramate's efficacy in reducing the frequency of heavy drinking days has been shown to be confined to C-allele homozygous carriers of the GRIK1 gene rs2832407 SNP, whereas there was no difference between topiramate and placebo for A-allele carriers[110]. This same SNP has been shown to be associated with topiramate side effects; carriers of the A-allele had more severe topiramate related side effects compared to those homozygous for the C-allele[111]. Pharmacogenetic advances have been made for other AUD treatment medications[120], as summarized in Table 1[121].

Table 1. Brief Review of Positive Findings of Genetic Influences in Alcohol Pharmacotherapy

	Genetic Variants	Moderates	Notable Studies
Topiramate	GRIK1(rs2832407)	% Heavy drinking days, Side effects	Kranzler, 2014 [110]; Ray, 2009 [111]
Naltrexone	OPRM1 (Asn40Asp), (rs1799971), DRD4 VNTR	% Heavy drinking days, abstinence rates, relapse to heavy drinking	Anton, 2008 [112]; Kim, 2009 [113]; Oslin, 2003 [114]; Tidey, 2008 [115]
Ondansetron	LL/LS/SS (5-HTTLPR) (rs1042173), SLC6A4 (5-HTTLPR)	Drinks per drinking day, % days abstinent	Johnson, 2011 [116]
Sertraline	5-HTTLPR tri-allelic SLC6A4	% Heavy drinking days % drinking days	Kranzler, 2011 [117]
Acamprosate	GATA4 (rs1327367)	Relapse	Kiefer, 2011 [118]
Disulfiram	DBH (rs161115)	Adverse Events	Mutschler, 2012 [119]

Genetic moderation has also been studied in medications acting on the serotonergic system with regard to their effects on alcohol consumption. Kranzler et al.[117] previously showed a moderating effect on sertraline treatment response by SNPs in the gene encoding the serotonin transporter protein (5-HTT) and age of onset of alcohol dependence. Similarly, 5-HTT gene polymorphisms are implicated in moderating ondansetron treatment response in early onset AUD patients[116]. Studies of other medications used to treat AUD, such as acamprosate and disulfiram have also yielded promising findings. For example, acamprosate response has been linked to polymorphisms of the GATA4 gene (regulating atrial natriuretic peptide)[118] and disulfiram-related adverse effects have been linked to functional polymorphisms of the dopamine-beta hydroxylase gene [119].

NAC's mechanisms of action include stimulation of mGluR2/3. The metabotropic Glu receptor 3 is a member of the mGlu2/3 family and has shown impact in animal studies of alcohol dependence[122-126], including attenuation of alcohol self-administration and cue-induced reinstatement[54]. A recent human study found significant differences in the allelic and genetic frequency of the A allele of SNP rs6465084 in the GRM3 region of an alcohol-dependent group compared to controls[127]. Genetic polymorphism associations of rs6465084 with AUD support mGlu2/3 as potential treatment targets and possible moderators of treatment outcome[127]. These genetic associations will be explored in the proposed project.

C.5. PRELIMINARY STUDIES IN THE ADDICTION RESEARCH PROGRAM AT THE SAN FRANCISCO VAMC

The PI's Addiction Research Program at the SFVAMC has been testing the efficacy of pharmacotherapies for

AUDs and has successfully completed a Department of Defense (DoD) funded pilot trial of *topiramate in veterans with AUD and PTSD*[128], the results of which led to the funding of a large (n=150) clinical trial in the same population.

Simultaneously, The PI obtained IMN funding for a preliminary investigation of *topiramate in veterans with HHAU and TBI*. Through the current conduct of this 12-week placebo controlled pilot trial of TOP in veterans with TBI and HHAU, we have built a strong alcohol clinical trials team, developed recruitment strategies, assessment procedures, and retention methods with an understudied and challenging veteran population. We plan to enroll a total of 32 participants over the course of 11 months, and at study midpoint we have enrolled 53%. Of those who met basic eligibility criteria, 37% (28/75) expressed reluctance to take prescribed psychotropic medication, often citing concerns about adverse effects. Offering an over-the-counter supplement such as NAC, will likely result in greater acceptability of treatment than that which we have experienced in the current trial of TOP in HHAU and TBI. TOP has a problematic adverse event profile[129], including transient reductions in learning and memory[128]. However, even with the barriers related to tolerability, our research team has been able to maintain high retention rates, with 81% completing the study, as defined by attending Week 12.

Using data gathered from our completed and ongoing clinical trials of topiramate, we examined the associations of baseline characteristics in 47 veterans with HHAU, PTSD with and without TBI. In group comparisons, there were no differences in drinking severity and groups were similar in PTSD symptom severity (Table 2). Groups were also similar in performance in various neurocognitive domains including risk-taking, motor inhibition, decision making, divided attention, auditory-verbal learning and memory, processing speed, working memory and verbal fluency[130]. *Within the TBI group, high risk taking was related to the consumption of more standard alcohol drinks per week, and worse decision-making was related to more heavy drinking days per week* (Table 3). Additionally, in the TBI group, higher total PTSD symptom severity was related to greater risk-taking and worse processing speed (Table 4).

Table 3. Significant (p<.047) correlations (r) between alcohol use, self-regulation and processing speed in TBI and [no-TBI]

Measure	DD/Wk	HDD/Wk	Drinks/Wk	Drinks/DD
BART Pumps Adj Avg.			.49	
IGT: Net Total t-score		-.72		
HVLT: Learning			[-43]	
Stroop Word	[-77]		[-.81]	[-.78]

Table 2. Patient demographics and AUD/PTSD characteristic in veterans with AUD and PTSD, with and without TBI (mean ± SD)

	TBI	no-TBI	p-value
n (female)	21 (2)	26 (2)	
Age	44.7 ± 12.7	52.0 ± 10.8	.040
Education	12.5 ± 2.3	14.3 ± 2.0	.007
Comorbid SUD (%)	5 (24%)	11 (42%)	NS
CAPS Total	75.1 ± 17.0	82.4 ± 16.2	NS
Intrusions	19.0 ± 5.3	21.7 ± 6.3	NS
Avoidance	30.1 ± 9.5	35.2 ± 8.6	.043
Arousal	26.5 ± 4.8	25.5 ± 5.1	NS
Drinking Days/Week (DD/Wk)	5.3 ± 1.8	5.8 ± 1.3	NS
Heavy Drinking Days/Week (HDD/Wk)	4.8 ± 1.9	4.8 ± 2.4	NS
Drinks/Week	65.8 ± 38.4	62.9 ± 41.4	NS
Drinks/Drinking Day	13.0 ± 6.3	11.1 ± 7.4	NS

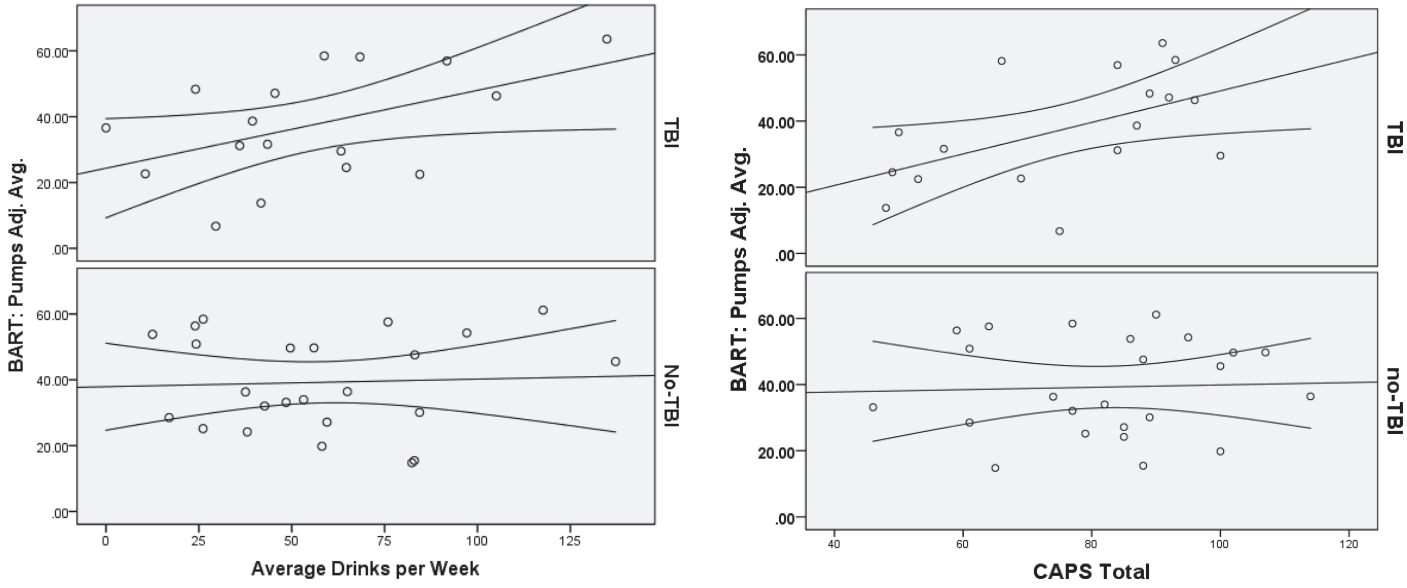
Heavy drinking day (>4 standard alcoholic drinks for men, >3 standard alcoholic drinks for women). Standard alcoholic drink is defined as containing 13.6 g of pure alcohol. Drink consumption was averaged over 90 days preceding study consent.

Table 4. Significant (p,.048) correlations (r) between CAPS PTSD symptoms and cognition in TBI and [no-TBI]

Measure	Total	Intrusion	Avoidance	Arousal
BART: Pumps Adj. Avg.	.52	.49		.50
BART: Explosions	.49			
Trails A			-.51	
HVLT: Learning		[-.45]		

As illustrated in Figure 1, we observed differences in associations between alcohol use, PTSD and measures of risk-taking between the TBI and no-TBI groups. Additionally, in the TBI group, higher frequency of drinking was associated with higher levels of danger-seeking[131]. NAC treatment could be hoped to lead to reduction in not just alcohol consumption, but possibly TBI symptom severity, and improved cognitive performance.

Figure 1.



C.6. INNOVATION

This pilot prospective, double-blind, placebo-controlled clinical trial of NAC treatment in 30 veterans with TBI and HHAU. It is necessary to obtain a preliminary determination of the efficacy, safety, tolerability, and feasibility of NAC in a pilot study before proceeding to a larger, more resource-intensive clinical trial. Moreover, the resources available from the IMN funding mechanism do not permit the conduct of a larger trial of NAC in TBI and HHAU, which, in any case, may be premature, given the questions regarding its efficacy, feasibility, and safety in the specific population to be studied. A placebo-controlled trial is justified because it is the standard in the field and there are no proven medications for concurrent TBI and HHAU. Our primary aims will be to measure both alcohol use and TBI symptom severity over the course of the 12-week study in order to detect differential efficacy of NAC and placebo. Alcohol use treatment outcome will be the Percent Days of Heavy Drinking (PHDD) of alcohol. A heavy drinking day is defined using NIAAA[8] (2007) criteria: any day with 5 or more drinks per day for men or 4 or more drinks per day for women[8]. The choice of PHDD as the primary outcome is based on its endorsement by a recent NIAAA consensus conference[9] and its increasing use in clinical trials [10-12]. TBI symptom severity will be measured with the Neurobehavioral Symptoms Inventory (NSI)[13,14], a measure of postconcussive symptom severity. Other exploratory aims will include obtaining additional measures of alcohol use, executive functioning (e.g., impulsivity and risk taking) and other domains of neurocognition, and examining the potential moderating effect of rs6465084 on NAC treatment response. To achieve these aims, we will conduct a pilot prospective, parallel groups, randomized, double-blind, placebo-controlled flexible-dose clinical trial of NAC in 30 veterans with TBI and hazardous or harmful alcohol use. The 8-week treatment phase will consists of treatment with NAC or placebo, plus weekly manualized alcohol counseling, added to whatever usual TBI treatment participants may be receiving, including medication (exceptions being any alcohol treatment medications). The manualized counseling for alcohol use disorders will consist of Medical Management[15], an NIAAA manual-driven, low-intensity supportive program to promote adherence to the medication regimen and retention. Participants will continue to receive usual care for TBI and

other medical and/or psychiatric disorders from their primary medical and mental health treatment providers. Participants will meet with research staff weekly to receive medication, counseling, and research assessments during the 8 weeks of study treatment. Participants will also be assessed at the week-12 follow-up visit.

D. RESEARCH DESIGN AND METHODS

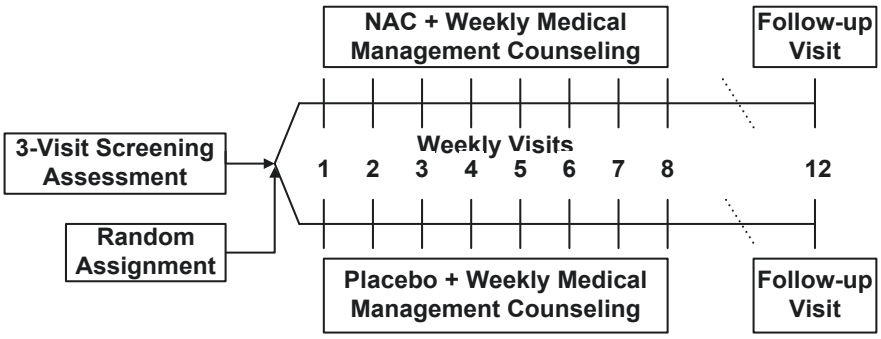
D.1. GENERAL DESIGN

D.1.a. Rationale for a Pilot Placebo-controlled Trial of NAC:

We propose a pilot prospective, double-blind, placebo-controlled clinical trial of NAC treatment in 30 veterans with TBI and HHAU. It is necessary to obtain a preliminary determination of the efficacy, safety, tolerability, and feasibility of NAC in a pilot study before proceeding to a larger, more resource-intensive clinical trial. Moreover, the resources available from the IMN funding mechanism do not permit the conduct of a larger trial of NAC in TBI and HHAU, which, in any case, may be premature, given the questions regarding its efficacy, feasibility, and safety in the specific population to be studied. A placebo-controlled trial is justified because it is the standard in the field and there are no proven medications for concurrent TBI and HHAU.

D.1.b. Overview of Design:

Our primary aims will be to measure both alcohol use and TBI symptom severity over the course of the 12-week study in order to detect differential efficacy of NAC and placebo. Alcohol use treatment outcome will be the Percent Days of Heavy Drinking (PHDD) of alcohol. A heavy drinking day is defined using NIAAA (2007) criteria: any day with 5 or more drinks per day for men or 4 or more drinks per day for women[9]. The choice of PHDD as the primary outcome is based on its endorsement by a recent NIAAA consensus conference[98] and its increasing use in clinical trials[99-101]. TBI symptom severity will be measured with the Neurobehavioral Symptoms Inventory (NSI)[102,103], a measure of postconcussive symptom severity. Other exploratory aims will include obtaining additional measures of alcohol use, executive functioning (e.g., impulsivity and risk taking) and other domains of neurocognition, and examining the potential moderating effect of rs6465084 on NAC treatment response. To achieve these aims, we will conduct a pilot prospective, parallel groups, randomized, double-blind, placebo-controlled flexible-dose clinical trial of NAC in 30 veterans with TBI and hazardous or harmful alcohol use. The 8-week treatment phase will consists of treatment with NAC or placebo, plus weekly manualized alcohol counseling, added to whatever usual TBI treatment participants may be receiving, including medication (exceptions being any alcohol treatment medications). The manualized counseling for alcohol use disorders will consist of Medical Management[106], an NIAAA manual-driven, low-intensity supportive program to promote adherence to the medication regimen and retention. Participants will continue to receive usual care for TBI and other medical and/or psychiatric disorders from their primary medical and mental health treatment providers. Participants will meet with research staff weekly to receive medication, counseling, and research assessments during the 8 weeks of study treatment. Participants will also be assessed at the week-12 follow-up visit.



D.2. STUDY PARTICIPANTS

D.2.a. Overview of Participants

Participants will be recruited from the San Francisco VA Medical Center and will be men and women, ages 18 through 69, with a diagnosis of mild TBI plus current (past month) alcohol use disorder.

We will recruit 30 participants from the San Francisco Veterans Affairs Medical Center (SFVAMC). Recruitment will be through direct outreach to patients via notices and cards in patient areas and asking clinicians to refer patients. Research staff will conduct brief pre-screening to assess possible eligibility. At the

SFVAMC, sites will include the Primary Care, Neurology, TBI, Mental Health and Substance Abuse clinics, and affiliated satellite clinics (Community-Based Outpatient Clinics [CBOCs] in Downtown San Francisco, Santa Rosa, CA, and San Bruno, CA), regional Vet Centers and mental health clinics. The Investigator and Research Coordinators will work with staff in outpatient units at the SF VAMC to explain the study, including eligibility criteria, potential risks and benefits to study involvement, how to refer a potential study candidate and how prospective participants can contact study staff. Once a prospective participant has been identified, research staff will conduct a brief telephone or in-person pre-screening interview to assess possible eligibility. If pre-screening is successful, research staff will obtain written informed consent and gather demographic and locator information including contact information for the patient's treatment providers. Written permission will be obtained for research staff to review mental health records and consult with the participant's primary care provider, psychiatrist, and other clinicians to obtain clinical information to assist in the assessments of medical status, psychiatric diagnoses, and substance use. The participant's primary care and/or mental health providers will also be asked for their assent to any patient entering the study.

This study will actively recruit women as participants. Specifically, non-pregnant females, ages 18 to 69, will be eligible to participate. Pregnant females will be excluded from the study because NAC's effects on the developing fetus is unknown and it is not known whether NAC is excreted in human milk.

We anticipate that the majority of research participants may be males due to the significantly higher prevalence of alcohol use disorders among men and due to the fact that the SFVAMC will be the major recruitment site. Based on our recruiting experience in our current research, we expect that approximately 10%-15% of participants in the project may be women as outlined in the female breakdown in the Targeted/Planned Enrollment Table. However, we hope to increase the recruitment rate of female participants as much as possible, by actively recruiting in the SFVAMC' Women's Clinic and other sites likely to have higher numbers of women.

The projected cohort is diverse and well-represented in ethnic categories of Hispanic or Latino and in the racial categories of African-American, Asian and Pacific Islander. This project will recruit members of minority groups in all of its research activities. A diverse population of study participants is expected to be recruited from the SFVAMC as it has a rich mix of ethnic/racial groups represented among the patient population. The anticipated ethnic and racial breakdown is outlined in the Targeted/Planned Enrollment Table. In addition, the clinical staff at the SFVAMC who help to recruit prospective participants are both ethnically and racially diverse.

Moreover, the current research staff in our lab are both men and women, as well as African-American, Asian, and Native American racial representation and both Hispanic and non-Hispanic ethnicity representation.

We will take a number of steps to emphasize the recruitment of women and minorities for this project. These include: a) encouraging clinicians to be particularly attentive to the identification of female patients and those of ethnic and racial minority who may be appropriate for, and benefit from, the study, b) continuing to hire a research team of diverse gender and ethnicity to increase the likelihood of recruiting prospective participants with diverse backgrounds, c) consulting with the appropriate diversity enhancement staff of UCSF/NCIRE, and SFVAMC to identify additional strategies designed to increase recruitment of women and minorities.

D.2.b. Inclusion Criteria

INCLUSION CRITERIA	
1.	Male and female Veterans eligible for VA services.
2.	Ages 18-69 (inclusive)
3.	A history of TBI, as defined by ACRM, in the chronic, stable phase of recovery (>6 months from injury). The ACRM defines TBI as a traumatically-induced physiological disruption of brain function, as manifested by **at least one of the following**: (3a) any period of loss of consciousness; (3b) any loss of memory for events immediately before or after the accident; (3c) any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or

	confused); **AND** (3d) focal neurological deficit(s) that may or may not be transient
4.	Current (within last 12 months) moderate (4-5 symptoms) or severe (6+ symptoms) alcohol use disorder by DSM-5 criteria.
5.	Current (past month [30 days]) Hazardous Alcohol Use: Hazardous use is drinking that meets NIAAA criteria[12]: Current (past 30 day) weekly drinking, consisting of an average ≥ 15 standard drinks/week for men or ≥ 8 standard drinks/week for women.
6.	Participants must express a desire to reduce or stop alcohol use.
7.	Female participants must have a negative urine pregnancy test and must be either postmenopausal ≥ one year or practicing an effective birth control method.
8.	Participants must have a Breath Alcohol Concentration (BAC) of 0.00% when signing the informed consent.

D.2.c. Exclusion Criteria.

EXCLUSION CRITERIA	
1.	Unstable psychotic or bipolar disorders, dementia, or other psychiatric disorders judged to be unstable in the clinical judgment of the PI or study physician.
2.	Clinically significant unstable medical conditions, in the clinical judgment of the PI or study physician.
3.	Female patients who are pregnant or nursing.
4.	Concurrent participation in another alcohol treatment study, or in any research study involving medications.
5.	Requiring acute medical detoxification from alcohol based on a score of 12 or more on the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-AD);
6.	NAC use in the past week prior to study entry.
7.	Use of AUD treatment medications (disulfiram, naltrexone, or acamprosate) within the past week.
8.	Participants who are legally mandated to participate in an alcohol treatment program.
9.	Participants who in the opinion of the investigator should not be enrolled in the study because of precautions, warnings or contraindications outlined in the NAC package insert.
10.	Participants who are taking the following medications that have been reported to have adverse drug-drug interactions with NAC: carbamazepine and nitroglycerin.
11.	Participants with known hypersensitivity to acetylcysteine.
12.	Participants with an increased risk of upper GI bleed (such as those with esophageal varices) that could be exacerbated by vomiting.
13.	Participants who have had a suicide attempt in the past 3 months or suicidal ideation, with intent, in the 30 days prior to enrollment.

D.2.d. Modification of Inclusion and Exclusion Criteria.
As of the modification submitted on 6/15/17, we are expanding our inclusion criteria to include Veterans with moderate and severe TBI. Expanding inclusion criteria to include Veterans with moderate and severe TBI.

We are requesting this revision in order to facilitate recruitment. Limiting inclusion to only those Veterans with mild traumatic brain injury (TBI) has slowed recruitment. Too many potential participants have been excluded because they have had TBI histories that cross into the moderate or severe TBI range.

Our original reason for excluding Veterans with moderate or severe TBI history included concerns about the possibility of residual medical, psychiatric or cognitive problems of such severity that study participation would be judged to be unsafe. In fact, many Veterans with moderate or severe TBI histories are stable medically, psychiatrically, and cognitively, and would be appropriate for safe study participation.

In the judgment of the study investigators, simply having a history of moderate or severe past TBI does not necessarily mean that patients have severe or unstable medical, psychiatric, or cognitive problems that would make study participation unsafe.

We therefore request approval for broadening of inclusion criteria to include all Veterans with TBI histories, whether mild, moderate or severe.

We propose continuing our present practice -- as per the current study protocol -- of excluding any potential participants who, in the opinion of the study physician, have medical, psychiatric, or cognitive problems judges to be too unstable or too severe to allow safe participation in the study.

As of the modification submitted on 9/25/17, we are expanding our inclusion criteria to include Veterans between the ages of 18 and 69, inclusive. Similar to the revision described above, we are requesting this revision in order to facilitate recruitment.

D.3. STUDY PROCEDURES

D.3.a. Overview of Study Procedures

The study has three phases: screening; 8-week treatment; Week-12 follow-up. The 8-week treatment phase will consists of treatment with NAC or placebo plus weekly Medical Management (MM), a manual-driven, low-intensity supportive program to foster, maintain and promote compliance with study medication and to promote continuation in the study, added to whatever usual treatment participants may be receiving (except AUD medication). Participants will meet weekly with research staff at the San Francisco VA Medical Center clinics.

D.3.b. Recruitment

The process for screening for eligibility will commence as soon as all approvals have been obtained from all regulatory bodies.

We will employ many methods to recruit 30 participants that meet inclusion and exclusion criteria.

Previous Participants
Participants that have participated in research studies conducted in the SFVAMC Addiction Research Program and who have opted in to be contacted about future research studies will receive a call from study staff.

Search of SFVAMC Medical Records
Study staff will search the SFVAMC medical records for veterans that have a co-occurring alcohol use disorder and a mild traumatic brain injury diagnosis. A study staff member will contact the care provider of the potential participant once identified. The care provider will be asked to inform the potential participant about the study, to gauge interest and assess the fit of the veteran for the study. If, and only if, a veteran expresses interest in the study to their care provider, then a member of the research team will initiate contact. To be clear, a potential participant will never be contacted about the study by anyone other than their direct (mental or primary) care provider until the potential participant gives verbal consent to be contacted. Providers are asked to tag the PI on notes placed in the medical record of Veterans who seem like they would be a good fit for the study, have expressed interest in the study and have agreed to a study staff member reaching out to Veteran with more information.

Presentations for and Emails Sent to Patient Care Providers:
Research staff will explain the purpose and scope of the study, including eligibility criteria, to care providers and will engage in a continuous process of publicizing the study. Hospital and clinic staff will be told whom to contact to refer a potential study candidate and how to have prospective participants contact study staff. Clinicians will receive brochures and/or handouts to pass out to their patients as they see fit. The primary care and mental health providers will also be asked for their assent to any patient entering the study.

Posted Recruitment Materials
Veterans may become aware of the study through posted recruitment materials placed in patient areas of the the clinics in the San Francisco VA Medical Center, as well as other VA Medical Centers in the San Francisco Bay Area. Materials will also be posted in the associated Community Based Outpatient Clinics (CBOCs) in San Bruno, San Rafael and the San Francisco VA Downtown Clinic.

Intake Screener
A brief, 3-question screener (**See Intake Screener**) asking about alcohol use, posttraumatic stress disorder (PTSD) diagnosis and the occurrence of a traumatic brain injury (TBI) will be passed out to veterans attending intake visits in the mental health and primary care clinics at the San Francisco VA Medical Center and CBOCs. Veterans will not be required to fill out the form if they are not interested in the study. If they are interested in the study, but do not want to fill out the screener, they may contact study staff directly via phone. If a veteran does complete the Intake Screener, he/she will be asked to place the screener in a sealed envelope and return to the front desk at the clinic. The screener-in-envelope will be placed in the VA inter-office mail folder and returned directly to study staff. Because the Intake Screener contains PHI (Last Name; Last 4 digits of social security number; and Phone Number) in addition to sensitive information concerning alcohol use, PTSD and TBI, we will follow the VA Directive 6609 and place the screener in an envelope labeled with **VA Directive 6609, Appendix B**, to ensure that special attention is given to the contents in the rare chance that it is intercepted or lost. When study staff receives an Intake Screener, it will be stored separately from de-identified data, in a locked cabinet in a locked room.

Opt-Out Packet
Packets will be mailed to potential participants identified by a referring clinician or through a medical record search. Packets will include an Opt-Out Letter, a Study Information Sheet, and an Opt-Out Postcard. The Opt-Out Letter will introduce the research study, explain how the PI obtained their name and addresses. The letter will provide a general, brief description of the research study and invite the recipient to call the lab manager if interested in learning more (see Opt-Out Letter). The opt-out packet will also include an information sheet describing the time commitment, compensation and other general details study participation (**See Information Sheet**). A pre-addressed, stamped postcard will be included in the letter which a patient can return to indicate that they do not wish to be contacted for this study (**See Opt-Out Postcard**).

Study staff will wait to contact potential participants for 2 weeks after the initial mailing to allow them time to opt-out if they do not wish to be contacted. If the team does not receive an "opt-out" postcard at least 14 days after the original mailing, then they will attempt to contact the veteran by telephone, but will adhere to strict confidentiality. Staff will speak only to the patient once identified. If study staff were to reach a non-study participant, he/she would state only that they are calling from the SFVAMC and will not disclose any information pertaining to the study. If a patient states that he/she does not wish to be in the study, staff will respectfully remove from the call list and never call again. If an opt-out letter is returned to the SFVAMC due to an incorrect mailing address, staff will try to make contact via phone. If staff are unable to reach a patient after 3 attempts, efforts will stop.

Clinical Trial Management Software (CTMS) Database
Study staff will access a pool of shared participants utilizing a password-protected database called Clinical Trial Management Software. Individuals in this database have been asked brief screening questions from a Program Wide Prescreen, which is described in depth in approved Protocol 12-09158, or from a specific study. Recruiters will contact individuals from this database who can decide if they want to answer the study specific screen. Informed consent will be obtained by research staff prior to beginning any procedures.

D.3.c. Prescreening
Prospective participants will undergo a brief CPRS pre-screen (**see CPRS Screen**) and an in-person or telephone pre-screen (**see Phone Screen**) to establish that they are: 18-69 years of age, screen positive for TBI, drink at hazardous or harmful levels by NIAAA criteria[8] and wish to reduce or stop alcohol use.

D.3.d. Consent
Breath Alcohol Test Prior to Consent
If the breath alcohol test reading is greater than 0.00%, the participant will be asked to return later that day, or on another day, to be retested.

Consenting
After passing the pre-screen, participants will provide written informed consent in compliance with IRB

regulations. During the consent process, Veterans are asked to abstain from driving to study visits while intoxicated. They are informed that if they do drive and their breath alcohol level is above 0.08, then a clinician will assess their safety before they are allowed to leave the SF VA Medical Center.

D.3.e. Screening
After consent, participants will be scheduled for screening assessments. The screening phase is accomplished over a total of approximately three to four visits extending over one week.

D.3.f. Random Assignment
Participants will be randomly assigned, sequentially as they qualify for the study, to either NAC or placebo in a 1:1 ratio per a computer-generated list provided by a biostatistician. Randomization will be balanced using permuted blocks. Participants and investigators will be blinded to assignment. To maintain the blind, sealed envelopes containing the study drug identification (e.g. NAC or placebo) will be kept together, in a limited access area (the study pharmacist's office) that will be available to the investigators should the blind need to be broken for any individual participant.

D.3.g. Pharmacotherapy
Random assignment will be followed by 8 weeks of treatment with NAC or placebo. Study medications will be identical in appearance. Participants will be provided with 10 days of medication at each weekly visit to increase the likelihood of medication continuity in case of a missed visit. Extra medication will be collected from participants at each visit. Study medication (NAC or placebo) will be started at a dose of 600 mg bid (1200 mg per day), for 3 days, then 1200 mg bid for 4 days, (2400 mg per day), then 1800 mg bid (3600 mg per day) for weeks 2 through 8. Similar doses have been shown to be an effective dose in other addiction studies (see A.2.). If the participant experiences significant side effects during the titration period, the dosage may be adjusted as necessary. Patients will be treated with the highest dose tolerated, not to exceed a total of 3600 mg per day, but may be reduced by 600mg increments as needed. Wellspring Compounding Pharmacy, a compounding Pharmacy – a compounding pharmacy recommended by the University of California, San Francisco School of Medicine Pharmacy -- will supply NAC study capsules and matching placebo capsules. The policies and procedures concerning good compounding practices and environmental, instrumental and procedural quality assurance have been approved by the California State Board of Pharmacy. The SFVAMC Research Pharmacist will directly receive all study medications from Wellspring Compounding Pharmacy and store in appropriate environmental conditions. The dosage is to be determined by a study physician at each weekly visit, using the titration schedule as a guide. An official VA prescription form must be filled out by a study physician for each patient at each visit. A research associate will pick up the prescription from the SFVAMC pharmacy. The date, time and amount of study compound dispensed will also be recorded in the subject's electronic medical file. Participants are instructed to return all unused study medication weekly. The number of returned capsules will be documented.

D.3.h. Medical Management
We selected a manualized version of the NIAAA Project COMBINE alcohol counseling, "Medical Management" (MM)[27]. This intervention helps increase problem recognition, enhance motivation, and facilitate engagement in alcohol treatment. Participants will receive weekly MM sessions for a total of 120-240 minutes consisting of 8 weekly individual sessions lasting 15-30 minutes each. The goal of MM is to help patients maintain adherence with the medication regimen using strategies that can be delivered by a typical health care provider. MM approximates a primary care approach to alcohol dependence and supports the use of pharmacotherapy. During the initial visit, the clinician reviews the patient's assessments, highlighting symptoms of alcohol use disorder and the need for treatment. The patient is advised to stop drinking, educated about unhealthy alcohol use, provided a rationale for taking the study compound, and instructed on the importance of daily medication adherence. The clinician and participant also jointly develop an individualized medication-adherence plan; the patient is encouraged to attend support groups and is given information on the medications. At follow-up visits, drinking behavior and medication adherence are ascertained, and plans for reducing drinking or achieving abstinence are revised as needed. In each session, the MM administrator will communicate and discuss medication effects, participants' concerns about any side effects and compliance barriers with the participant in understandable terms. Training will be provided to the research MD, RN and psychologist who will be MM administrators. The PI and his appointees will monitor MM

sessions and provide training and guidance to the MM administrators as needed.

D.3.i. Measures and Schedule of Data Collection Overview

All alcohol, substance use, psychiatric, and medical measures are validated and reliable, and are only briefly outlined below due to space limits. Efforts to reduce missing data will include use of: (a) collateral informants to assist in locating participants; (b) telephone contact for missing participants; (c) flexible time periods for the completion of assessments.

Measures of Health/Biological Safety

Baseline *blood draw* (genetics). *Urine pregnancy* at baseline, Wks 4 & 8. A participant who becomes pregnant during participation in the study will be withdrawn. *Vital signs, weight, concomitant medications, suicide risk assessment*[133], *adverse events (AEs)*, and *alcohol withdrawal* (Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD)[134] will be monitored weekly.

Alcohol and Substance Use Measures

Time-Line Follow-Back (TLFB)[135,136] for alcohol and drug use covering the 90 days prior to entry, then at Wks 1-8, and 12. TLFB will be used to calculate the primary outcome measure, PHDD, and exploratory alcohol measures of percent drinking days, drinks per drinking day, etc. Standard drink conversions will be used for participant reports of alcohol consumption[8]. Cigarette and other substance use will also be collected by TLFB[137]. The Intoximeters Alco-Sensor IV instrument will be used for *Breath alcohol concentration (BrAC)*[138] at each weekly visit. The following measures will be at baseline, Wks 4, 8 and 12: *Obsessive Compulsive Drinking Scale (OCDS)*[139] as an exploratory measure, assesses thoughts and compulsions associated with alcohol craving; *Urine Drug Screen* for opioids, cocaine, cannabis, and methamphetamine at baseline; *Ethyl Glucuronide (EtG),* a direct metabolite of ethanol[140] used to provide an exploratory objective biological measure alcohol use within the last 80 hours; *Gamma Glutamyl Transpeptidase (GGT),* a marker for alcohol consumption[141], will provide a biological measure of heavy alcohol use.

Traumatic Brain Injury Symptoms

Neurobehavioral Symptoms Inventory (NSI)[13,14], a measure of postconcussive symptom severity at baseline, Wks 4, 8 and 12.

Psychiatric Diagnosis/Psychological Measures

Baseline:

- *Structured Clinical Interview for DSM-IV, (SCID-I/P)*[142]: Alcohol and other substance use diagnoses will be established using the Substance Use Disorders (SUDs) module of the SCID I/P[143]. The SCID-I/P is the standard SCID-I designed for research participants identified as psychiatric patients.

The following measures will be at baseline, Wks 4, 8 and 12:

- The *PTSD Checklist (PCL)*[145], a self-report measure PTSD symptom severity over the prior 30 days
- *Beck Depression Inventory*[146]*:* provides a measurement of depression severity[147]
- *Beck Anxiety Inventory (BAI)*: a measure of anxiety severity[148]; well suited for monitoring change with treatment[148]

Neurocognitive Assessment

The battery was developed to assess performance in cognitive domains commonly affected by TBI and/or alcohol use and contains standardized instruments with good-to-excellent norms administered (~1.5 hours) at baseline, Wks 4,8 and 12. Domains and constituent measures:

- *Risk Taking, Decision-making, and Motor/Choice Impulsivity:* Balloon Analogue Risk Task[149-151]; Iowa Gambling Task[152]; Stop-signal[153], Delayed Discounting[154-158]
- *Executive Functioning:* Stroop Color-Word[159,160], Trail Making B[161]
- *Verbal Fluency*: Controlled Oral Word Association Test[162]
- *Processing Speed*: Trail Making A[161], Stroop Color-Word[159,160]
- *Working Memory:* WAIS-IV Arithmetic and Digit Span[163]
- *Learning and Memory:*
  - *Auditory-verbal:* Hopkins Verbal Learning Test (HVLT-R)[164]
  - *Visuospatial:* Brief Visual Memory Test-Revised[165,166]

- *Premorbid verbal intelligence*: Wechsler Test of Adult Reading[167,168]
- *Alcohol Approach Bias*: Alcohol Approach Task (AAT)[209]

Raw scores are converted to z-scores based on norms. Domain-specific summary score will be calculated by averaging z-scores of the constituent measures. To minimize practice effects, when feasible, alternate forms will be used for repeated administrations.

Statistical Plan and Data Analysis
The proposed study has primary and exploratory outcomes.

Primary Outcome
The *Primary* hypotheses are that NAC treatment will be more efficacious than placebo in reducing PHDDs and TBI symptom severity (NSI). Data analytic technique: *Percent Heavy Drinking Days (PHDD):* Negative binomial regression accommodates over dispersion and derives as an alternative to Poisson regression (most natural for analyzing count data). Heavy percent drinking days is often over-dispersed, positively skewed count data. Therefore, we will use random-intercept zero-inflated negative binomial model, modeling week (week 1 - week 8) as a continuous variable to analyze group differences in PHDD. *Neurobehavioral Symptom Inventory (NSI):* We will use random-intercept linear mixed models to explore the efficacy for NAC related reduction in TBI symptom severity measured by the NSI. Time period will be treated as a repeated effect, with correlations between time periods within participants modeled by an unstructured correlation matrix where appropriate. Model assumptions will be tested and required modifications will be performed. Both models will included fixed effect for week, treatment group (NAC and placebo), and the interaction between treatment group and week. Baseline alcohol consumption and NSI means will be used as respective covariates in group comparisons to control for pre-study and study enrollment effects.

Exploratory Outcomes
Our exploratory hypotheses are that NAC treatment will be more efficacious than placebo in reducing other measures of alcohol use, producing significant improvement in cognitive performance (see section H.4.e), and will be moderated by rs6465084. Data analytic technique: Exploratory hypotheses will be analyzed in a parallel fashion, with separate negative binomial models applied to non-normally distributed count data and mixed linear models used for the remaining normally distributed outcome measures. Assumptions of each model will be tested and any required modifications will be performed. To investigate the potential moderating effect of rs6465084, we will use linear mixed models crossing treatment group with a two-level genotype group (A-allele vs. non A-allele carriers)[110,121], looking for a treatment group-by-genotype interaction on PHDD, and other secondary exploratory outcome measures of alcohol use.

Multiple Comparisons
Adjustment for multiple comparisons will be made for the separate families of primary outcomes (PHDD, NSI, cognitive performance) using a modified Bonferroni method[169].

Estimates of NAC vs placebo for a larger study of HHAU and TBI.
We plan to derive a reliable estimate of effect for planning a large RCT from this small controlled pilot study. It will be useful to obtain estimates of variability in order to inform future controlled trials of NAC treatment for alcohol use. Our sample of n=30, with power of .80 will have the ability to detect an effect size of approximately .65 (one-tailed, alpha = .05). This is conventionally considered a medium effect size. To test for efficacy, we plan to implement intent-to-treat analyses, therefore including all participants randomized to trial. To examine estimates of harm, we will complete Per-Protocol analyses using data from participants exposed to study medications.

Study Limitations/Potential Problems.

Recruitment, retention, missing data, and safety issues have been the most difficult hurdles facing clinical trials in AUDs. We believe that our research team is demonstrating a high level of success in recruiting (See Table 5) and retaining similar participants with TBI and HHAU, with 81% of participants completing the PI's pilot trial of TOP, a medication with a much higher adverse event profile[129]. Similarly, there has been little missing data, with 81% of weekly study visits attended. Moreover, the use of a mixed-effects model allows for all available data in model estimation. Finally, human participant safety, although a prime concern, is relatively low in the use of NAC[170] (See Human Subjects Section)

Table 5. PI's current trial of topiramate in HHAU and mTBI	
Prescreened	**255**
Screened (Signed Consent)	**25**
Randomized	**17 (53%)**
Percent Visits Attended	**80.88%**
Percent Attended Week 12	**81.25%**

D.3.j. Phlebotomy and Urine Drug Testing

Phlebotomy will be performed at screening, week 4, 8, and 12. Urine drug testing will be performed at screening, week 4, week 8, and week 12.

D.3.k. Participant Payment

Participants will be compensated in cash or check for their time, effort and travel costs after each completed visit. The screening visits at baseline will be reimbursed based on the completion of tasks up to $85. The payment schedule for baseline/screening measures and procedures is listed below. Participants will receive $20 for completed visits on Weeks 1, 2, 3, 5, 6, and 7. The longer visits of Weeks 4 and 8 will be compensated at a rate of $35 and the follow-up visit $40. Participants will also be paid $5 at each study visit during weeks 1-8 for returning study medication bottles. Additionally, if participants attend all 9 study visits, they will receive an additional $50 at the follow-up visit. Details regarding compensation are outlined below and in the informed consent form. Participants can therefore earn up to a total of $410 for the full 12-week study participation.

If a participant lives outside of the San Francisco city limits and it takes over an hour to get to the SFVAMC, then the participant will receive $0.51 per mile (NCIRE travel reimbursement policy). Mileage will be calculated using the Google maps "DIRECTIONS" function, using the participant's home address as the starting point and the SFVAMC address as the point of destination.

PAYMENT SCHEDULE FOR BASELINE/SCREENING MEASURES/PROCEDURES

MEASURES/PROCEDURES	AMOUNT
Informed Consent	---
TLFB/Patient Locator	$10
SCID	$5
TBI Evaluation	$10
CTSI	$10
Self-report measures – (21 total)	$20
Neurocog	$20
Med Mgmt	$5
AEs/ConcomMeds/Concom Txt	$5
TOTAL AMOUNT	$85

WEEKLY COMPENSATION SCHEDULE

Week	Attend study visit	Return MEMS cap	Attend all study visits	Total per visit
Screening Visits	$85*			$85
Week 1	$20	$5		$25
Week 2	$20	$5		$25
Week 3	$20	$5		$25
Week 4	$35	$5		$40

Week 5	$20	$5		$25
Week 6	$20	$5		$25
Week 7	$20	$5		$25
Week 8	$35	$5		$40
Week 12	$40		$50	$90
POTENTIAL TOTAL AMOUNT PAID				$405

D.4. MEASURES AND SCHEDULE OF DATA COLLECTION

D.4.a Overview (See Table 1 for Schedule of Measures)

Efforts will be made toward reducing the amount of missing data by: (a) use of a collateral informant to assist in locating patients; (b) telephone follow-up to make contact with missing patients; (c) establishment of flexible, but acceptable, time periods for the completion of each assessment; and (d) some self-report and interview measures may be administered by telephone to collect missing data from patients unwilling or unable to visit research sites to participate in a scheduled assessment session. All phone visits will include a Medical Management counseling session, during which a trained psychologist or psychiatrist (the Medical Manager) will assess adverse effects, concomitant medications, suicidality and general well-being. During phone visits, study coordinators will skip the question on the Adverse Event checklist, “Have you had suicidal thoughts or actions since the last study visit”. Instead, the Medical Manager will ask that question and report back to coordinator after the Medical Management counseling session. If a Medical Management counseling session becomes logistically impossible, the PI will file a protocol violation.

Establishment of flexible, but acceptable time frames for completion of research assessments:
All research assessments should be completed within an established window. Assessments scheduled for weeks 1, 2,3,5, 6, and 7 will have a window of ±3 days for completion. Assessments scheduled for weeks 4, 8, and 12, have a window of ±1 week for completion. This flexibility will enhance the ability of staff to schedule patients for assessments as close as possible to the protocol defined period. Patients likely to miss appointments should be scheduled early in the window to allow for successive attempts to complete ratings within the desired time frame.

After receiving CHR and R&D approval, we will be converting most of our questionnaire measures to a digital format, so that this questionnaire data can be collected and managed using the San Francisco VA Medical Center’s Stress and Health Research Program Data Management Research Database System.

The Research Database System will include FDA regulated and non-regulated research studies. The SQL Server Database Engine is the core service for storing, processing, and securing data within the enterprise. Clinical study databases built in sql server also have a data change tracking mechanism, (i.e. audit trail) identifying data changes made by who, when, what changed, and reason for change.

Electronic data transfer is serviced from a number of external computer applications where data points are generated and stored based on a participant interfacing with a computer application. Implementation of process flow allows the transfer of data between the sql server database and a wide variety of data formats. Additional safeguards include using user authentication to access data on the research server. Different user profiles allow access to specific tables of the sql server database. For example, investigators and their research staff can view and edit data on their own participants only. Furthermore, unique study identification numbers are used to identify participants on data forms and transmitting participant names or other identifying information over the internet is not permissible.

The central system consists of a Dell PowerEdge 2970 mid-range server. Its features include 4GB of RAM and storage allocated to provide 72GB for the operating system and 145GB for the data. There are 2 quad-core processors installed. For fault tolerance and redundancy the server has five 73GB hard drives.

Operating system installed with Microsoft Windows Server 2003 R2 and SQL Server 2005 database server for processing and housing of clinical data. Microsoft Internet Information Services (IIS) functions as the Web Server for intranet use.

For backup and disaster recovery of the system and data, a dedicated Dell PowerVault LTO-3 tape drive is employed along with Symantec Backup Exec 2010 R3 as the management software. The LTO-3 system has a capacity (per tape) of 400GB native / 800GB compressed. Backup tape media is encrypted to comply with the Federal Encryption Standard, FIPS-140-2 and stored offsite in a secure vault.

The server is located in the SFVAMC Information Research Management Systems (IRMS) server room which has 24-hour surveillance, restricted access and resides within the SFVAMC firewall, providing an extra level of security. This room has air-conditioning units, and provides battery backup in case of a power failure. The server is also kept current with virus protection software and security patches. The server components have been validated through a series of installation, qualification and performance protocols.

There are future plans to bring in an additional server machine configured as an application server as well as a library tape system.

Study management is further supported by a Clinical Trial Management System (CTMS) application providing the ability to track many aspects of a clinical trial. Study start-up includes numerous administrative and clinical activities. All of these tasks involve tedious, manual process for collecting and aggregating information from different data sources. The CTMS system consolidates these efforts (i.e. reduce duplications and inconsistencies) and provide efficiencies and cost savings for the clinical operations. Users also manage recruitment outreach activities, track recruitment progress, and search through a pool of potential participants for future studies. The system provides real-time and comprehensive study management metrics to support the day-to-day business operations. This CTMS system is a commercial off-the shelf product that hooks into the research database server for added data integration.

D.4.b. General Measures

D.4.b.1. PATIENT SCREENING LOG
Written informed consent will be obtained prior to screening for study eligibility and completion of baseline assessments. All patients who undergo eligibility screening will be listed on the Patient Screening Log to provide information about the number of patients screened.

D.4.b.2. PATIENT LOCATOR INFORMATION
This form includes information about how to contact the participant.

D.4.b.3 BASELINE ASSESSMENTS
Measures will be recorded on several forms and will include demographic information (such as age, gender, race, and ethnicity), work history, medical history, physical examination, laboratory evaluation DSM-IV psychiatric diagnoses, alcohol, substance use, and cigarette smoking history, current medications, and family history.

D.4.b.4 ELIGIBILITY FORM
The listing of inclusion and exclusion criteria will serve as a screening format for eligibility which will be completed following baseline assessments.

D.4.b.5. MAINTENANCE OF THE BLIND
This questionnaire is administered at Week 12 to assess the maintenance of participants' and physicians' blindness. Participants are asked to speculate on their assignment to either topiramate or placebo. Each participant's treating physician is also asked to speculate on the participant's assignment to topiramate or placebo.

D.4.b.6. STUDY COMPLETION/TERMINATION FORM

This form is to be administered upon completion of the study (as defined by attending Week 12 visit) or at termination to document the last day of study medication ingestion, number of visits attended and/or reasons for terminating.

D.4.b.7. PARTICIPANT – END-OF-STUDY QUESTIONNAIRE
This measure is administered at Week 12 to assess the participant's opinion of participation and what was helpful/useful during treatment.

D.4.c. Measures of Health/Biological Safety

D.4.c.1. OVERVIEW OF HEALTH/BIOLOGICAL SAFETY MEAUSURES
Safety evaluations will include: entry medical history and physical examination, weekly vital signs monitoring, weekly breath alcohol concentration (BrAC), weekly CIWA-AD (clinical alcohol withdrawal assessment), weekly monitoring for adverse events, suicide risk assessment at baseline, periodic clinical laboratory tests (complete labs including urinalysis at baseline, periodic renal function and liver function tests, and urine pregnancy tests performed every 28 days on women of childbearing potential.

D.4.c.2. MEDICAL HISTORY AND PHYSICAL EXAMINATION
A medical history and physical examination will be completed at baseline during the screening period. Study physicians will screen medical records. This information will be recorded on the physical examination form.

D.4.c.3. CLINICAL LABORATORY TESTS FOR HEALTH AND SAFETY MONITORING
The following tests will be performed by the San Francisco VAMC clinical laboratory.

Clinical laboratory tests at baseline (Screening phase):
Blood samples will be collected for serum chemistry, liver panel (LFTs), renal panel and complete blood count (CBC) and a urine sample will be collected for urinalysis, and, for women – urine pregnancy test.

If AST or ALT are >5 times the upper limit of the normal range, or if serum bilirubin is >2 times the upper limit of normal, these tests will be repeated, and if the repeat tests still exceed these limits, the participant will be excluded.

Clinical laboratory tests for health and safety monitoring throughout the study:
Renal and hepatic panels will be repeated at Visits 4 and 8 for all participants.

D.4.c.4. BIRTH CONTROL/PREGNANCY ASSESSMENT
Birth Control/ Pregnancy Assessment will be done at baseline/screening at weeks 4, 8, and 12. Any participant who becomes pregnant during participation in the study will be withdrawn. The results will be recorded on a Birth Control/pregnancy Assessment Form.

D.4.c.5. VITAL SIGNS
Vital signs (temperature, heart rate, and blood pressure) will be measured weekly. Weight will be monitored monthly. The results will be recorded on a Vital Signs Form.

D.4.c.6. CONCOMITANT MEDICATIONS
All concomitant medications (prescription or over-the-counter medications) taken at the time of screening as well as those started during the study will be documented on a Concomitant Medication Form completed weekly.

D.4.c.7. CONCOMITANT TREATMENT
All concomitant treatments for mental health and well-being, with a focus on alcohol and substance use, PTSD and TBI will be recorded on a monthly basis. At screening, participants will be asked to report on the history of the mental health treatment. At weeks 4, 8, and 12 they will be asked to report on any new treatments they have started while in the study. Information will be recorded on the Concomitant Treatment form.

D.4.c.8. ADVERSE EVENT (AE) MONITORING

All adverse events that occur between the first study-related procedure and the last study-related procedure will be reported. Serious adverse events occurring within 30 days following the last dose of study medication will also be handled according to this procedure. Those meeting the definition of serious adverse events will be reported using the Serious Adverse Event Form. Active monitoring of Adverse Events (AEs) will begin as soon as a study participant initiates study treatment, and will continue until the end of study for each participant. AEs will be monitored weekly in two ways:

a. An open-ended question will be asked about presence of any AEs weekly (AE Spontaneous).
b. A checklist of expected topiramate-related AEs will be asked of each participant weekly (AE Checklist).

All Adverse Events will be recorded on the appropriate forms.

D.4.d. Alcohol and Substance Use Measures

D.4.d.1. TIMELINE FOLLOWBACK (TLFB)

Alcohol and drug use will be assessed using the Time-Line Follow-Back (TLFB))[135,136]. This is a self-report test which will be performed at baseline/screening and will cover the 12 weeks prior to entry, with particular attention to the 4 weeks immediately preceding entry to the study. In addition, the TLFB will be done weekly for the preceding 7 days at weeks 1-8, and at week 12. The TLFB will be used to calculate percent of days abstinent from alcohol, drinks per drinking day, and percent heavy drinking days. The (TLFB) is a method to assess the quantity of alcohol consumption on a daily basis. With a calendar as a guide, the participant provides a retrospective estimate of daily drinking over a specified period. For this study participants will estimate their daily drinking for the 28-day period prior to the initial screening and for the 7-day period prior to each weekly visit. The TLFB provides a calendar of the targeted period for recording the number of standard drinks consumed on each day. The TLFB can be used to obtain the number of days on which drinking occurred and the number of drinks per day. Standard Drink Conversions will be used to standardize all participant reports of alcohol consumption [8].

The following variables will be derived from the standard drinks consumed per day: 1) Percent Days Abstinent (the number of non-drinking days divided by the number of study days) 2) Percent Heavy Drinking Days (the number of days for which the number of drinks was at least 5 drinks for men and at least 4 drinks for women, divided by the number of study days); 3) Drinks/Day (the number of drinks consumed divided by the number of study days); and 4) Drinks/Drinking Day. The TLFB will be administered in interview format. It takes 5-10 minutes to complete the TLFB for a 28-day period. Interviewers require no clinical expertise but some training. Prior to reviewing alcohol use, the interviewer will prepare the TLFB calendar outlining the time period to be assessed and noting holidays and other general important or newsworthy events that have occurred (e.g., Super Bowl Sunday). During Screening and at each weekly visit thereafter, participants will be provided with a diary card for recording the number of drinks consumed each day. The diary is intended as a memory aid and interviewers should discuss and verify any information collected on the diary and verify if any days without entries are actually non-drinking days or drinking occurrences that were not recorded. Differences will be discussed with the participant and the site personnel will clarify the number of drinks per day.

Cigarette (Brown et al. 1998) and other non-alcohol substance use will also be collected using the Timeline Followback. Participants are shown the same calendars used for Alcohol TLFB and asked to use recall to record the number of cigarettes smoked and days of cannabis, cocaine, opiate, and methamphetamine use. Cigarette and other non-alcohol substance use TLFB data will be collected at baseline for the previous 28 day time period. Data will also be collected at each subsequent visit for the time since the last visit. Purpose: To calculate the primary outcome measure, PHDD. To assess alcohol use frequency and amount on a daily basis, in order to calculate percent of days abstinent from alcohol, drinks per drinking day, and percent heavy drinking days and to assess cigarette and other non-alcohol substance use frequency.

Time required for administration: The initial assessment requires 10-15 minutes; subsequent weekly administration takes 5 minutes. Frequency of administration: Baseline and weekly during weeks 1-8 and week 12.

D.4.d.2 OBSESSIVE COMPULSIVE DRINKING SCALE (OCDS)

The Obsessive Compulsive Drinking Scale (OCDS) assesses obsessive thoughts and compulsions associated with alcohol craving using a 14-item self-report scale[171]. The OCDS is a modification of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and is designed to measure these thought patterns and behaviors in heavy drinkers. Each question has five possible answers scored on a scale of 0-4. A higher score indicates a greater level of obsessive compulsive drinking. The 14 items will be divided into 4 empirically derived factors[172] The first factor, Drinking Obsessions is composed of 4 variables (items 1-4) that address obsessive thoughts related to drinking. The second factor, Alcohol Consumption, consists of 2 items (items 7 and 8) which evaluate the quantity and frequency of alcohol consumption. The third factor, Automaticity of Drinking contains 5 variables (items 5, 6, 12, 13 and 14) which assess the extent to which drinking was controlled or uncontrolled. The fourth factor, Interference, is comprised of 3 items (items 9, 10 and 11) which evaluate the extent to which drinking interferes with work and social functioning, and the degree to which being prevented from drinking is distressing. The same 14 items will also be summed to produce a total score, an Obsessive Thoughts subscale score, and a Compulsive Drinking subscale score. It takes approximately 5 minutes to complete the OCDS. Purpose: To provide data for descriptive purposes and a secondary outcome relating to drinking and as an exploratory measure that assesses thoughts and compulsions associated with alcohol craving. Time required for administration: 5 minutes. Frequency of administration: The OCDS will be administered at baseline screening and weeks 4, 8, and 12.

D.4.d.3. BREATH ALCOHOL CONCENTRATION (BrAC)

The breath alcohol concentration (BrAC) will be measured at each session to detect recent alcohol use. The *Intoximeters Alco-Sensor IV* instrument will be used to measure breath alcohol at each visit to ensure that participants are not acutely intoxicated. This instrument is approved by the US Department of Transportation for evidential use; it meets and exceeds the federal model specification for traffic enforcement and Omnibus Breath Alcohol Testing[138].

It must be determined that the participant has a BrAC of 0.00% in order to sign the informed consent.

At subsequent visits, if the participant's BrAC is greater than 0.025%, study clinician will assess whether or not the participant may complete the study visit. The participant may be asked to wait until the breathalyzer test is lower, or he/she may be asked to complete the visit at another time. If the participant is unwilling or unable to remain at the site until their BrAC returns to 0.025%, study medication will be dispensed but additional study procedures will not be completed. Breath Alcohol Concentration (BrAC) –will be measured weekly. Study visits that include neurocognitive testing require complete sobriety (0.00%). If a participant's BrAC is greater than 0.00% the participant will wait until BrAC returns to normal or complete the visit on another day. Purpose: To ensure that the participant is sober enough to perform the required study activities. Time required for administration: 1 minute. Frequency of administration: This test will be administered at each weekly visit.

D.4.d.4. URINE DRUG SCREEN (UDS)

Urine Drug Screen (UDS): Urine drug testing for opioids, cocaine, cannabis (THC), and amphetamine/methamphetamine at baseline. The test will be performed by the SF VAMC Clinical Laboratory. Purpose: To provide data for descriptive purposes, and provide data for exploratory outcomes on substance use other than alcohol. Time required for administration: Collecting the urine sample should take less than 5 minutes. Analysis may take 1 to 3 days (estimate). Frequency of administration: The urine drug screens are conductet at baseline screening and weeks 4, 8, and 12.

D.4.d.5. ETHYL GLUCURONIDE (EtG)

Ethyl Glucuronide (EtG), is a non-volatile, water-soluble, stable, direct metabolite of ethanol that is currently used in clinical research for alcohol treatment to detect recent alcohol use, up to approximately 80 hours post consumption[140]. EtG is considered a sensitive and specific marker that enables detection of small amounts of alcohol in cases where neither traditional biological state markers of alcohol intake nor clinical impression gave an indication for lapse or relapse[173]. EtG also validates self-report measures such as TLFB and AUDIT. Purpose: To provide an objective biological measure that detects recent alcohol consumption and verifies self-reported alcohol use within the last 80 hours. Time required for administration: Collecting the urine

sample, packing, storing, and shipping should take less than 15 minutes. Once 20 samples have been collected they will be sent to a remote processing center. Test results will be received 1 to 2 weeks from the shipment date (estimate). Frequency of administration: The EtG will be conducted at baseline screening and weekly.

D.4.d.6. GAMMA GLUTAMYL TRANSPEPTIDASE (GGT)
GGT is currently the most widely used marker for alcohol consumption. GGT has been found to be elevated in patients with chronic heavy alcohol consumption and in a variety of liver conditions unrelated to drinking and therefore is not specific to alcohol consumption. GGT levels generally rise after heavy alcohol intake that has continued for several weeks. 50-72% of elevated GGT levels can be explained by excessive alcohol consumption (Sillanaukee, 1996). We will measure GGT on a Vitros 950 with a normal range for males of 15-73 U/l and for females of 12-43 U/l. Purpose: To provide an objective biological measure as a secondary measure of alcohol use. Time required for administration: Collecting blood sample should take 5-10 minutes. Lab analysis will take 1-3 days. Frequency of administration: At baseline screening and weeks 4, 8, and 12.

D.4.d.7. PHOSPHATIDYLETHANOL (PEth)
According to a combination of research, analysis demonstrates good efficiency of PEth for detecting chronic heavy drinking[174]. It is considered a mid to long-term alcohol biomarker, and a positive result is an indication of alcohol exposure the 2-3 weeks prior to sample collection. During a series of processes, Phosphatidylethanol (PEth) accumulates in human red blood cells when the body is exposed to ethanol. Since it is formed only when the body is exposed to ethanol it is called a direct alcohol biomarker. The accumulation in red blood cells make it easy to test by collecting blood specimens. Purpose: : To provide an objective biological measure as a secondary measure of alcohol use the 2-3 weeks prior to the test. Time required for administration: 5 minutes Frequency of administration: At Week 12

D.4.d.8. PENN ALCOHOL CRAVING SCALE (PACS)
The Penn Alcohol Craving Scale (PACS) is a self-report measure that is used to assess alcohol craving, without directly asking about craving's aversive quality or incentive properties [175]. Number of items: 5 items. Time required for administration: 3 minutes. Frequency of administration: Weeks 0, 4, 8, 12.

D.4.d.9. ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)
The Alcohol Use Disorders Identification Test (AUDIT) has been developed from a six-country WHO collaborative project as a screening instrument for hazardous and harmful alcohol consumption. It covers the domains of alcohol consumption, drinking behavior, and alcohol-related problems. It provides a simple method of early detection of hazardous and harmful alcohol use in primary health care settings [176]. Number of items: 10 items Time required for administration: 5 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.d.10. SHORT INDEX OF PROBLEMS (SIP 2-R)
The Short Index of Problems is an alternate short version of the 45-item assessment Drinker Inventory of Consequences (DrInC). These items were chosen to represent lifetime consequences of alcohol use. [177] Number of items: 15 items Time required for administration: 5 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.d.11. CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT FOR ALCOHOL (CIWA-AD)
The Clinical Institute Withdrawal Assessment for Alcohol is for clinical quantitation of the severity of the alcohol withdrawal syndrome. The scale is administered by trained study staff [178]. Number of items: 10 items Time required for administration: 3 minutes Frequency of administration: The CIWA will be conducted at baseline and at the beginning of every weekly visit.

D.4.d.12. FAMILY TREE QUESTIONNAIRE (FTQ)
This brief, self-report questionnaire is used to assess the family history of drinking problems. The questionnaire was designed to provide participants with a consistent set of cues for identifying relatives with drinking problems [179]. Number of items: At least 6, asked to identify drinking history of maternal and paternal grandparents, parents, and brothers and sisters. Time required for administration: 3 minutes Frequency of administration: Week 0

D.4.d.13. THOUGHTS ABOUT ABSTINENCE (TAA)
The Thoughts About Abstinence is designed to assess the participant's thoughts related to alcohol. It measures the desire to quit, expected success in quitting and estimated difficulty in avoiding relapse. It also assesses the participant's goal for use raning from no goal to complete abstinence for life [180]. Number of items:4 items Time required for administration: 5 minutes Frequency of administration: Week 0

D.4.d.14. READINESS TO CHANGE RULER (RTC)
The Readiness to Change Ruler is a quick, self-report measure that asks the participant to identify where they are on the continuum of motivation readiness to change their drinking behavior [181]. Number of items: 1 item. Time required for administration: 1 minute Frequency of administration: Week 0

D.4.d.15. SUBJECTIVE HIGH ASSESSMENT SCALE (SHAS)
A self-rated adjective checklist to assess the effects of alcohol on mood and levels of intoxication. The items includes questions aobut the positive effects of alcohol and the negative aspects of intoxication [182]. Number of items:38 items Time required for administration: 10 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.d.16. ALCOHOL PURCHASE TASK (APT)
The Alcohol Purchase Task presents a scenario and asks participants how many drinks they would purchase and consume at different prices. The measure aims to assess the relative value of alcohol and measure of risk for alcohol problems [183]. Number of items 27 items Time required for administration: 3 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.e.TBI Measures

D.4.e.1. NEUROBEHAVIORAL SYMPTOM INVENTORY (NSI)
In accordance with the recommendation of the Review Committee, we are specifying the inclusion of the Neurobehavioral Symptom Inventory (NSI) as a measure to quantify symptoms associated with mild traumatic brain injury. The NSI evaluates common complaints associated with mild TBI and post-concussive syndrome. The NSI asks patients to rate how much various symptoms have disturbed them in the last two weeks. While it is not a diagnostic test, the constellation of symptoms has been validated for mild TBI, and the NSI is useful in developing a clinical profile (Cicerone & Kalmar, 1995; Meterko et al., 2012). Cicerone and Kalmar developed this 22-item self-report inventory of symptoms commonly observed among patients with mild TBI. The NSI, based on the Cicerone and Kalmar tool, is utilized by the Veterans Administration in the evaluation of returning OEF/OIF veterans. The 22 items of the NSI are embedded within the VA's Secondary TBI Evaluation that is conducted for all veterans entering the VA who have not been previously diagnosed with TBI, but who screen positive for possible TBI.
We will analyze the results to detect both within-group changes in the Topiramate arm of the study as well as between-groups differences between the Topiramate and Placebo groups over the course of the study.
Purpose: To quantify symptoms associated with mild traumatic brain injury. Time Required for administration: 5-10 minutes. Frequency of administration: The NSI will be administered at baseline and weeks 4, 8, and 12.

D.4.f. PTSD Measures

D.4.f.1. PTSD CHECKLIST (PCL)
The PCL (Weathers et al., 1994) is a 17-item self-report questionnaire that prompts informants to endorse the level of distress that has co-occurred with each reported PTSD symptom over the prior 30 days. A five point scale is used for informant responding (1 = *not at all, 5 =extremely)*[185]. The PCL has been demonstrated to possess good internal consistency, test-retest reliability, convergent validity, and discriminant validity (Ruggiero, 2003). The short administration time also makes it useful in settings where it might need to be administered multiple times. Purpose: To assess PTSD symptom severity. Time required for administration: Approximately 5 minutes (Ruggiero, 2003). Frequency of administration: at baseline screening and weeks 4, 8, and 12.

D.4.g. Psychiatric/Psychological Measures

D.4.g.1. STRUCTURED CLINICAL INTERVIEW FOR DSM-IV-TR, PATIENT EDITION (SCID-I/P)
Alcohol and other substance use disorder diagnoses will be established by administering the Substance Use Disorders (SUDs) diagnostic module of the SCID I/P (First et al., 2001) combined with a review of clinical records, information from the primary therapist and/or psychiatrist. The SCID-I/P is a clinician-administered, semi-structured interview for use with psychiatric patients. The SCID-I/P is the standard SCID-I designed for research participants identified as psychiatric patients (Ventura, 1998). The interview begins with an overview section that obtains demographic information, work history, chief complaint and past periods of psychiatric illness, treatment history, and assessments of current functioning with open ended questions to elicit response in the participant's own words. The interview provides required probe questions and suggested follow-up questions. Liberal use of skip-out directions are employed when a participant fails to meet a critical criterion required for a particular disorder. Purpose: To identify eligible potential participants. Time required for administration: The SUDs module of the SCID-I/P takes approximately 30 minutes to complete. Frequency of administration: This test will be administered at the screening visit.

D.4.g.2. BECK DEPRESSION INVENTORY (BDI)
Depression will be measured with the Beck Depression Inventory (Beck et al., 1961). The BDI is a 21-item, self-report questionnaire that provides a measurement of depression severity. Each item is rated on a four-point scale (absent, mild, moderate, or severe). It has demonstrated high internal consistency and good concurrent validity with other measures of depression (Beck et al, 2000) Purpose: To assess participant depression severity before, during, and after topiramate or placebo treatment. Time required for administration: 5-10 minutes. Frequency of administration: at baseline screening and weeks 4, 8, and 12.

D.4.g.3. BECK ANXIETY INVENTORY (BAI)
The BAI is a 21-item self-report questionnaire designed to evaluate symptoms such as nervousness and inability to relax using a 4-point likert scale (Beck et al., 1988). The BAI has been proven to be a reliable and well-validated measure of anxiety symptoms and is well suited for monitoring change with treatment (Beck, 1988). Purpose: To assess participant anxiety severity before, during, and after topiramate or placebo treatment. Time required for administration: 5 minutes. Frequency of administration: at baseline screening and weeks 4, 8, and 12.

D.4.g.4. DIFFICULTIES IN EMOTION REGULATION SCALE (DERS)
The Difficulties in Emotion Regulation Scale (DERS) is a brief, self-report questionnaire designed to assess multiple aspects of emotion regulation. The measure yields a total score as well as scores on six scales derived through factor analysis: nonacceptance, goals, impulse, awareness, strategies, clarity[188]. Number of items: 36 items Time required for administration: 8 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.g.5. DISTRESS TOLERANCE SCALE (DTS)
The Distress Tolerance Scale is a self-report measure of emotional distress tolerance[189]. Number of items: 15 items Time required for administration: 5 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.g.6. INSOMNIA SEVERITY INDEX (ISI)
The Insomnia Severity Index is a brief screening measure of insomnia. Number of items: 7 items Time required for administration: 3 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.g.7. PITTSBURGH SLEEP QUALITY INDEX (PSQI)
The Pittsburgh Sleep Quality Index is a self-rated questionnaire which asses sleep quality and disturbances over a 1-month time interval [190]. Number of items: 19 items Time required for administration: 5 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.g.8. PROFILE OF MOOD STATES (POMS)
The Profile of Mood States instrument is used to assess the mood states of individuals. Scales include anger-hostility, confusion-bewilderment, depression-dejection, fatigue-inertia, tension-anxiety, vigor-activity, and friendliness [191] [192].Number of items:65 items Time required for administration: 15 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.h. Neuropsychological Assessment

The neuropsychological battery tt will be used in this study was developed to assess performance in the cognitive domains commonly affected by mild TBI and alcohol abuse.

The overall battery of neuropsychological tests will take approximately 1.5 hours, with allowances for breaks. All neuropsychological test data will be scored based on standardized age and when available educational and repeated administration norms, and transformed into z scores for consistency. To assess the impact of training on targeted cognitive domains, and reduce the variability and number of multiple comparisons, z scores of individual neuropsychological tests will be averaged into the Cognitive Domain Scores.

To minimize adverse practice affects, whenever feasible, alternative test forms for repeated testing will be used for repeated administrations.

D.4.h.1. DECISION-MAKING ASSESSMENTS

D.4.h.1.a. IOWA GAMBLING TASK (IGT)
The Iowa Gambling Task (IGT)[203] is a measure of decision making, considered to be a behavioral manifestation of executive functioning. Participants are presented with 4 decks of cards on a computer screen and are told that they can win money by picking cards from the most advantageous deck. After each deck selection, participants are provided feedback as to whether their selection resulted in a "win" or a "loss" and the dollar amount of the win/loss. Its validity has been established in a number of studies examining decision-making abilities with a variety of populations, including substance users. The test generates a continuous score representing the dollar amount that the participant has at the end of the task. Purpose: To test decision-making processes so as to track how it changes over the course of the study and/or examine how it relates to topiramate/placebo, alcohol use and mild TBI. Number of items: Participants will choose a single card from 4 decks of cards. This process is repeated approximately 100 times. Time required for administration: 15 to 20 minutes. Frequency of administration: This test will be administered at baseline screening and weeks 4, 8, and 12.

D.4.h.1.b. DELAY DISCOUNTING (DD)
The second behavioral measure of impulsivity will be a delay discounting task of the type used in a number of previous experiments (Baker, Johnson, & Bickel, 2003; Bickel et al., 1999; Coffey et al., 2003; Kirby et al., 1999), using hypothetical rewards. In this task, participants will be asked to choose between a smaller immediate monetary reward and a larger delayed monetary reward. The behavioral principles guiding this task suggest that a pattern of choosing more immediate, smaller rewards over delayed, larger rewards indicates impulsivity (e.g., choice of $25 today over $100 in one month). Following a study conducted in Bickel's laboratory (Baker et al., 2003), the monetary rewards will be in $2 increments between $2 and $100. Delays for the later reward option will be 1 day, 1 week, 1 month, 6 months, 1 year, 5 years, and 25 years. On a computer screen, the participant will be shown, one at a time, hypothetical amounts that could be received immediately, while the hypothetical $100 reward will be displayed continuously. The "delay duration" will indicate the waiting period for the $100 delayed reward. The computer will randomly present each immediate reward amount, one at a time and respondents are asked to choose between each immediate reward or the delayed $100. Immediate reward amounts will be presented randomly. The computer will calculate the indifference point, the point at which delayed and immediate rewards are equally valuable to the participant. The same procedure will be repeated for each of the delay periods. Multiple studies have found that participants do not respond in a systematically different way to real and hypothetical rewards [193] [194]. Purpose: To measure risk-taking as an exploratory outcome variable. Time needed: 10 minutes. Frequency of administration: This test will be administered at baseline screening and weeks 4, 8, and 12.

D.4.h.2. RISK-TAKING ASSESSMENTS

D.4.h.2.a. BALLOON ANALOGUE RISK TASK (BART)

The Balloon Analogue Risk Task (BART; Lejuez et al., 2002, 2003), is a behavioral measure of impulsivity and risk taking developed by Carl Lejuez at the University of Maryland, College Park. Dr. Lejuez's research has shown that riskiness scores on the BART are positively related to self-reports of substance use and health and safety risk behaviors (Lejuez et al., 2002). The BART (Lejuez et al., 2002, 2003) was selected for its merits as a behavioral indicator of impulsivity and its simple, intuitive interface for lower-functioning participants. The BART displays a computer-generated balloon on the monitor of a desktop computer. The participant uses the click of a mouse to gradually inflate the balloon. Each click adds 5 cents to a temporary bank, the contents of which are not displayed. After each click, the participant has two options, 1) to continue to inflate the balloon at the risk of bursting it and losing all of the money from that balloon, or 2) saving the accumulated money to a permanent bank. Whenever a balloon bursts or the participant chooses to bank money, he or she starts with a new balloon. Participants respond to 30 balloons, each having a different bursting point. With each click, the participant must weigh the potential gain of collecting more money against the potential risk of losing all of the money accumulated with that balloon. The index of riskiness is based on the average number of clicks across balloons. The entire 30-trial task takes approximately 10 minutes to complete.

The instructions to the participant will be as follows: "Throughout the task, you will be presented with 30 balloons, one at a time. For each balloon you can click on the button labeled "Press This Button to Pump Up the Balloon" to increase the size of the balloon. You will accumulate 5 cents in a temporary bank for each pump. You will not be shown the amount you have accumulated in your temporary bank. At any point, you can stop pumping up the balloon and click on the button labeled "Collect $$$." Clicking this button will start you on the next balloon and will transfer the accumulated money from your temporary bank to your permanent bank labeled "Total Earned." The amount you earned in the previous balloon is shown in the box labeled "Last Balloon." It is your choice to determine how much to pump up the balloon, but be aware that at some point the balloon will explode. The explosion point varies across balloons, ranging from the first pump to enough pumps to make the balloon fill the entire computer screen. If the balloon explodes before you click on "Collect $$$," then you move on to the next balloon and all money in your temporary bank is lost. Exploded balloons do not affect the money accumulated in your permanent bank. At the end of the task, you will receive cash in the amount earned in your permanent bank." (Lejuez, 2002, pp. 78-79). Purpose: To measure risk-taking as an exploratory outcome variable. Number of Items: 30 balloons. Time needed: The BART can be completed in approximately 15 minutes. Frequency of administration: The BART will be given at baseline screening and weeks 4, 8, and 12.

D.4.h.2.b. EVALUATION OF RISKS (EVAR-B)

Used to assess risk-taking propensity in military samples. A series of risk-related statements are presented to the participant, who is asked to mark a point along the line that best represents his/her current sentiment for each risk-related statement[195]. Number of items: 24 items Time required for administration: 8 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.h.3. COGNITIVE FUNCTIONING ASSESSMENTS

D.4.h.3.a. WAIS-IV DIGIT SPAN

The WAIS-III Digit Span measures a person's ability to concentrate while manipulating mental mathemateical problems [196]. Purpose: To measure working memory in order to detect neurocognitive deficits that may accompany topiramate or placebo use, mild TBI, and alcohol use. Number of items:. 15 items Time required for administration: 10-15 minutes Frequency of administration: This test will be administered at baseline screening and weeks 4, 8, and 12.

D.4.h.3.b. WAIS-IV ARITHMETIC

The WAIS-III Arithmetic measures a person's attention, concentration and mental control[196]. Purpose: To measure working memory in order to detect neurocognitive deficits that may accompany topiramate or placebo use, mild TBI, and alcohol use. Number of items: 20 items Time required for administration: 10-13 minutes Frequency of administration: This test will be administered at baseline screening and weeks 4, 8, and 12.

D.4.h.3.c. CONTROLLED ORAL WORD ASSOCIATION (COWA):

The Controlled Oral Word Association is another assessment used to measure the performance of complex

attention and executive functioning; specifically, verbal fluency. During the test the examinee is asked to generate words that begin with a specified letter for one minute (phonemic fluency); and to generate words that belong to a specified category (semantic fluency)[160] Purpose: To measure verbal fluency in order to detect neurocognitive deficits that may accompany topiramate or placebo use, mild TBI, and alcohol use. Number of items: This test consists of three letter associations as well as two category associations. Time required for administration: 10 minutes. Frequency of administration: This test will be administered at baseline screening and weeks 4, 8, and 12.

D.4.h.3.d. HOPKINS VERBAL LEARNING TEST (HVLT)

Performance on Verbal and Visual Memory tests will be assessed with Hopkins Verbal Learning Test (HVLT-R)[164], requiring participants to learn 12 words after 3 learning trials and to recall them after 25 minutes. The Hopkins Verbal Learning Test (Brandt, 1991) was developed to briefly assess verbal recall and recognition. It consists of three learning/free-recall trials followed by a yes/no recognition trial [197]. Test stimuli are 12 words, four from each of three semantic categories. In the recognition trial, the 12 target words are interspersed among 12 distractor words. Six distractor items are high frequency exemplars of the same semantic categories as the target words, and six more are from other semantic categories. Because of these features the HVLT is well suited to repeated assessments (e.g., drug trials, tracking recovery from traumatic head injury or ECT) or where time constraints allow for only a brief assessment of new learning. The domains tested by the Hopkins are verbal recall and recognition (memory). Test–retest correlations of the HVLT are similar to other verbal memory tests, like the Logical Memory subtest of the Wechsler Memory Scale—Revised and the California Verbal Learning Test [198]. Other studies of the HVLT support its alternate form and test–retest reliability and its construct and content validity. The HVLT's reliability and validity has also been demonstrated in patients with head injury, schizophrenia, and dementia (Kuslansky, 2004). Purpose: To measure verbal memory and recall in order to detect neurocognitive deficits that may accompany topiramate or placebo use, mild TBI, and alcohol use. Number of items: 12 words are shown to participant 3 times (learning trial / free recall). This is followed by a recognition trial (Rasmusson, 1995). Time needed: 10 minutes or less (Rasmusson, 1995). Frequency of administration: This test will be administered at baseline screening and weeks 4, 8, and 12.

D.4.h.3.e. TRAIL MAKING TEST (TMT) PARTS A & B

The Trail Making Test, or TMT, was created as part of the Army Individual Test Battery [199]. Since then it has been widely used as an easily administered test of visual conceptual and visuomotor tracking [200]. Since it was developed by the U.S. Army, it is in the public domain and can be reproduced without permission. The test is given in two parts, A and B. The participant is first asked to draw lines connecting consecutively numbered circles on one work sheet (Part A), and then they are asked to connect the same number of consecutively numbered and lettered circles on a different worksheet, alternating between the two sequences (Part B). The participant is asked to connect the circles as fast as they can, without lifting the pencil from the paper. Scores are based on the amount of time the participant needs to complete the test. The most common scoring method is the one created by Reitan [201] in which the examiner points out errors as they occur, so that the participant can complete the test without errors. Then the score is based on time alone [202]. The domain tested by the TMT is tests complex visual scanning with a motor component [203]. Scores on the TMT are reliably sensitive to overall intelligence, neurological impairment, and age (Brown, 2006), and the TMT has been shown to be effective at discriminating between Vietnam combat veterans with and without PTSD [204]. It also has excellent interrater reliability (Brown, 2006). Purpose: To measure neurocognitive deficits that may accompany topiramate or placebo use, mild TBI, and alcohol use. Number of items: Participant connects 25 encircled numbers in part A, and another 25 encircled numbers in part B. Time needed: A cutoff time of 300 seconds is generally used to discontinue test administration and is therefore the typical maximum score [205]. Frequency of administration: Will be administered at baseline screening and weeks 4, 8, and 12.

D.4.h.3.f. WECHSLER TEST OF ADULT READING (WTAR):

Intellectual functions estimate will be assessed at baseline with Wechsler Test of Adult Reading- WTAR: The purpose of the WTAR is an estimation of pre-morbid intellectual ability. The examinee is asked to read a list of 50 words that have a typical grapheme to phoneme translations. Reading recognition is relatively stable in the presence of cognitive decline associated with brain injury[206]. Purpose: To gain a baseline estimation of intellectual functioning in order to examine how it relates to topiramate or placebo, mild TBI, and/or alcohol use. Number of items: The examinee is asked to read out loud 50 words which are compared to given

pronunciations and tallied for a total score of words read correctly. Time required for administration: 5 to 10 minutes Frequency of administration: The test will be administered at baseline screening and weeks 4, 8, and 12.

D.4.h.4. IMPULSIVITY ASSESSMENTS

D.4.h.4.a STROOP INHIBITION
The Stroop Inhibition[160] is another assessment used to measure the performance of complex attention and executive functioning; specifically, inhibition of automatic responding. The Stroop Inhibition (time and error score)[160] in which words are printed in dissonant ink color, and participants are instructed to name the color of the ink instead of the automatic response of reading the word. Purpose: To measure inhibition of automatic responding, an executive functioning task that is thought to be affected by alcohol use and mild TBI. Number of items: There are three, single page forms that participants will be instructed to read from. These sheets consists of a Word Page with color words printed in black ink, a Color Page with 'Xs' printed in color, and a color-Word Page with words from the first page printed in colors from the second page (the color and the word do not match).Time required for administration: 5 minutes. Frequency of administration: This test will be administered at baseline screening and weeks 4, 8, and 12.

D.4.h.4.b. STOP-SIGNAL TASK (SST)
The Stop Signal Task is a test designed to provide a measure of an individual's ability to inhibit an impulse. During the test, participants are instructed to respond as fast as they can to symbols such as letters or arrows presented on a computer screen. An auditory tone, which indicates to the participant that they are to withhold their response, accompanies a portion of these symbols. The tone occurs at various latencies after the appearance of the symbol on the computer and is randomized for each participant.
The SSRT, stop signal reaction time, is an estimation of the time an individual needs to stop their usual behavior (Striking a key every time they see the corresponding symbol) in response to the stop signal.
Purpose: To measure the ability of a participant to inhibit thought and action over the course of the study in order to examine how inhibition relates to topiramate or placebo, alcohol use and mild TBI. Time required for administration: 20 minutes. Frequency of administration: This test will be administered at baseline, as well as weeks 6, 12, and 16.

D.4.h.4.c. BARRETT IMPULSIVITY SCALE (BIS-11)
Barratt Impulsiveness Scale is a questionnaire designed to assess the personality/behavioral construct of impulsiveness [207]. It is the most widely cited instrument for the assessment of impulsiveness and has been used to advance our understanding of this construct and its relationship to other clinical phenomena. The items of the measure describe common impulsive and non-impulsive behaviors and preferences. The measure was created with the vision that impulsivity is a multifaceted construct and this multi-dimensionality is reflected in the structure of the measure. Number of items: 30 items Time required for administration: 5 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.4.h.5. ALCOHOL APPROACH BIAS ASSESSMENT

D.4.h.5.a. ALCOHOL APPROACH TASK
A non-training version of the Alcohol-AAT will measure automatic approach tendency toward alcohol at baseline and Week-4. This differs from our training AABM in that every picture will be presented in both formats (push landscape, pull portrait). The task starts with 10 practice trials showing neutral objects, followed by 80 test trials. A standardized d-score is calculated which represents differences in reaction time for pushing vs. pulling[209]. Negative values indicate less attentional bias[209]. Number of items:90 Time required for administration: 20 minutes Frequency of administration: Weeks 0, 4, 8, 12.

D.5. WEEKLY VISIT SCHEDULE

D.5.a. Screening Phase: Prescreening, Consent, Screening and Baseline Assessments
Each participant's participation in the study begins with the Screening Phase, consisting of approximately 3 visits over roughly 1 week, during which participants are evaluated for entry into the study. After the participant

passes the brief Prescreening Questionnaire (done in person or over the telephone), a consent form will be given to the participant to read and an oral explanation of the procedures will be given allowing the participant time to ask questions and consider study participation. Once the participant has agreed to participate in the study, a signed and dated informed consent will be obtained before any study-related procedures are performed. Each participant will be provided a copy of his/her signed and dated informed consent.

PRESCREENING
CPRS Prescreen
Phone Prescreen

CONSENT
Informed Consent
HIPAA
Research Subject's Bill of Rights
Patient Locator

SCREENING PHASE – BASELINE MEASURES + PROCEDURES The following baseline measures and procedures will occur during approximately 3 visits over roughly 1 week and take approximately 4.5 to 7 hours to complete.
Measures
Eligibility Form
Review of Medical History
TLFB - Timeline Followback
Concurrent Medications Form
Concurrent Treatments Form
AE Spontaneous Form
AE Checklist Form
SCID – Structured Clinical Interview for DSM-5 (Patient Edition)
Demographics
TBI Evaluation
CIWA – Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD)
Suicide Risk Assessment
NSI – Neurobehavioral Symptom Inventory
AUDIT – Alcohol Use Disorders Identification Test
SIP-2R – Short Index of Problems
OCDS – Obsessive Compulsive Drinking Scales
PACS – Penn Alcohol Craving Scale
FTQ – Family Tree Questionnaire
TAA – Thoughts About Abstinence
RTC – Readiness to Change Ruler
SHAS – Subjective High Assessment Scale
EVAR-B – Evaluation of Risks Scale
PCL – PTSD Checklist
POMS – Profile of Mood States
BDI-II – Beck Depression Inventory
BAI – Beck Anxiety Inventory
BIS-11 – Barratt Impulsivity Scale
PSQI – Pittsburgh Sleep Quality Index
ISI – Insomnia Severity Index
DERS – Difficulties in Emotion Regulation Scale
DTS – Distress Tolerance Scale
APT – Alcohol Purchase Task
WTAR - Wechsler Test of Adult Reading
HVLT-R – Hopkins Verbal Learning Test

TMT A + B – Trail Making Test A & B
WAIS 4 – Arithmetic
WAIS 4 – Digit Span
Stroop Inhibition
COWA – Controlled Oral Word Association
BART – Balloon Analogue Risk Task
IGT – Iowa Gambling Task
SST – Stop Signal Task
AAT – Alcohol Approach Task
Medication Dispensing Form
Procedures
Breath Alcohol Concentration (BrAC)
Physical Exam
Clinical Labs – renal panel, hepatic panel and GGT
Ethyl Glucuronide (EtG)
Urine Drug Screen
Blood draw for genetics (optional)
Vitals (Blood pressure, heart rate, temperature)
Weight
Medical Management
Assess birth control method and perform urine pregnancy test (women only)
Review Medical Event Monitoring System (MEMS)
Drug Accountability
Dispense Medication

Following completion of Screening Phase: Lab Manager will review inclusion/exclusion criteria. If eligible, the participant will proceed to the Treatment Phase.

Randomization assignment occurs at the end of Screening Phase.

D.5.b. Treatment Phase

TREATMENT PHASE – WEEKS 1, 2, 3, 5, 6, 7, 9, 10, 11 The measures and procedures collected and performed at these visits requires approximately 1 to 1.5 hours, the shortest amount of time relative to other visits.
Measures
TLFB – Timeline Followback
Concurrent Medications Form
AE Spontaneous Form
AE Checklist Form
CIWA – Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD)
Medication Dispensing Form
Procedures
Breath Alcohol Concentration (BrAC)
Ethyl Glucuronide (EtG)
Vitals (Blood pressure, heart rate, temperature)
Weight
Medical Management
Review Medical Event Monitoring System (MEMS)
Drug Accountability
Dispense Medication

TREATMENT PHASE – WEEKS 4, 8 The intermediate visits occurring on weeks 4 and 8 include some measures and procedures that were

originally collected at baseline/screening to ensure safety and allow for subsequent points of comparison. These visits are estimated to take between 3 – 3.5 hours to complete.
Measures
TLFB – Timeline Followback
Concurrent Medications Form
Concurrent Treatments Form
AE Spontaneous Form
AE Checklist Form
CIWA – Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD)
NSI – Neurobehavioral Symptom Inventory
AUDIT – Alcohol Use Disorders Identification Test
SIP-2R – Short Index of Problems
OCDS – Obsessive Compulsive Drinking Scales
PACS – Penn Alcohol Craving Scale
SHAS – Subjective High Assessment Scale
EVAR-B – Evaluation of Risks Scale
POMS – Profile of Mood States
BDI-II – Beck Depression Inventory
BAI – Beck Anxiety Inventory
BIS-11 – Barratt Impulsivity Scale
PSQI – Pittsburgh Sleep Quality Index
ISI – Insomnia Severity Index
DERS – Difficulties in Emotion Regulation Scale
DTS – Distress Tolerance Scale
APT – Alcohol Purchase Task
HVLT-R – Hopkins Verbal Learning Test
TMT A + B – Trail Making Test A & B
WAIS 4 – Arithmetic
WAIS 4 – Digit Span
Stroop Inhibition
COWA – Controlled Oral Word Association
BART – Balloon Analogue Risk Task
IGT – Iowa Gambling Task
SST – Stop Signal Task
AAT – Alcohol Approach Task
Medication Dispensing Form
Procedures
Breath Alcohol Concentration (BrAC)
Clinical Labs – renal panel, hepatic panel and GGT
Ethyl Glucuronide (EtG)
Urine Drug Screen
Vitals (Blood pressure, heart rate, temperature)
Weight
Medical Management
Assess birth control method and perform urine pregnancy test (women only)
Review Medical Event Monitoring System (MEMS)
Drug Accountability
Dispense Medication

D.5.c. Follow-up Phase

FOLLOW-UP PHASE The last visit, or follow-up, will take place on week 12. This visit will last between 3 and 3.5 hours.

Measures
Concurrent Medications Form
Concurrent Treatments Form
AE Spontaneous Form
AE Checklist Form
TLFB – Timeline Followback
Demographics
CIWA – Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD)
NSI – Neurobehavioral Symptom Inventory
AUDIT – Alcohol Use Disorders Identification Test
SIP-2R – Short Index of Problems
OCDS – Obsessive Compulsive Drinking Scales
PACS – Penn Alcohol Craving Scale
SHAS – Subjective High Assessment Scale
EVAR-B – Evaluation of Risks Scale
PCL – PTSD Checklist
POMS – Profile of Mood States
BDI-II – Beck Depression Inventory
BAI – Beck Anxiety Inventory
BIS-11 – Barrett Impulsivity Scale
PSQI – Pittsburgh Sleep Quality Index
ISI – Insomnia Severity Index
DERS – Difficulties in Emotion Regulation Scale
DTS – Distress Tolerance Scale
APT – Alcohol Purchase Task
WTAR - Wechsler Test of Adult Reading
HVLT-R – Hopkins Verbal Learning Test
TMT A + B – Trail Making Test A & B
WAIS 4 – Arithmetic
WAIS 4 – Digit Span
Stroop Inhibition
COWA – Controlled Oral Word Association
BART – Balloon Analogue Risk Task
IGT – Iowa Gambling Task
SST – Stop Signal Task
AAT – Alcohol Approach Task
End of Study Completion Questionnaire
Procedures
Breath Alcohol Concentration (BrAC)
Clinical Labs – renal panel, hepatic panel and GGT
Ethyl Glucuronide (EtG)
Urine Drug Screen
Phosphatidylethanol (PEth)
Vitals (Blood pressure, heart rate, temperature)
Weight
Assess birth control method and perform urine pregnancy test (women only)
Drug Accountability
Dispense Medication

D.6. DATA ANALYSIS

The proposed study has primary, secondary, and exploratory outcomes.

D.6.a. Primary Outcome Measure

The primary outcome measure will be the change in number of drinking days from baseline to end of study, associated with NAC treatment.

1) Primary Hypothesis
The *Primary* hypotheses are that NAC treatment will be more efficacious than placebo in reducing PHDDs and TBI symptom severity (NSI).

2) Data Analytic Technique for the Primary Outcome
Percent Heavy Drinking Days (PHDD): Negative binomial regression accommodates over dispersion and derives as an alternative to Poisson regression (most natural for analyzing count data). Heavy percent drinking days is often over-dispersed, positively skewed count data. Therefore, we will use random-intercept zero-inflated negative binomial model, modeling week (week 1 - week 8) as a continuous variable to analyze group differences in PHDD. *Neurobehavioral Symptom Inventory (NSI):* We will use random-intercept linear mixed models to explore the efficacy for NAC related reduction in TBI symptom severity measured by the NSI. Time period will be treated as a repeated effect, with correlations between time periods within participants modeled by an unstructured correlation matrix where appropriate. Model assumptions will be tested and required modifications will be performed. Both models will included fixed effect for week, treatment group (NAC and placebo), and the interaction between treatment group and week. Baseline alcohol consumption and NSI means will be used as respective covariates in group comparisons to control for pre-study and study enrollment effects.

3) Power Analyses for the Primary Outcome
We conducted a power analysis on our current pilot study of topiramate treatment of *alcohol dependence* in veterans with PTSD (see Section C.2.b.). For the outcome measure of percent drinking days (PDD), the effect size from the pilot data comparing week 12 to baseline within the topiramate group is d = 1.87. Because the proposed project is focused on veterans with TBI who have *hazardous* as well as harmful alcohol use, rather than just harmful use (alcohol dependence), we assume that the participants may start at a lower baseline level of DD in the proposed study than in the pilot study. This may not allow us to show as much improvement in the proposed study as in the completed pilot study of PTSD and alcohol dependence. Therefore, it would seem reasonable to target an effect size approximately half of what we found in our pilot study, i.e. d=0.9. A sample size of 16 for the topiramate arm of our proposed placebo-controlled pilot will allow us to detect a within-subjects effect size of d = 0.9, with 80% power at alpha = .05.

D.6.b. Exploratory outcomes/exploratory hypotheses

1) Exploratory Hypotheses
Our exploratory hypotheses are that NAC treatment will be more efficacious than placebo in reducing other measures of alcohol use (see section H.4.b), producing significant improvement in cognitive performance (see section H.4.e), and will be moderated by rs6465084.

2) Data Analytic Technique for the Exploratory Aims
Exploratory hypotheses will be analyzed in a parallel fashion noted in H.5.a., with separate negative binomial models applied to non-normally distributed count data and mixed linear models used for the remaining normally distributed outcome measures. Assumptions of each model will be tested and any required modifications will be performed. To investigate the potential moderating effect of rs6465084, we will use linear mixed models crossing treatment group with a two-level genotype group (C-allele vs. non C-allele carriers)[110,121], looking for a treatment group-by-genotype interaction on PHDD, and other secondary exploratory outcome measures of alcohol use.

D.7. TIME SEQUENCE

The study is expected to last 24 months. The first 2 months leading up to the start of the project through the second month of Year 01 will be devoted to start-up activities including hiring and training the research and clinical personnel, establishing the procedures and logistical aspects of conducting the clinical trial in the five

sites, obtaining all UCSF IRB, DoD, VA, and other regulatory approvals, and identifying the first study participants. Participant recruitment and randomization will begin in Month 3 of Year 01. At an average rate of about 2 participants per month, recruitment will take approximately 17 months. Delivery of intervention will begin in Month 3 of Year 01 and end in Month 19. The last of the follow-up appointments will be finished by the end of Month 23. In the final month of Year 02, we will concentrate on data cleaning, data analysis and preparation presentations and publications.

E. HUMAN PARTICIPANTS RESEARCH CONCERNS

E.1. PROTECTION OF HUMAN PARTICIPANTS

The PI will be responsible for following adverse event reporting requirements as outlined below in the protocol. These responsibilities include reviewing the accuracy and completeness of all adverse events reported; compliance with IRB policies for reporting adverse events and serious adverse events; reporting any safety issues to the IRB; and closely monitoring research volunteers at each study visit and telephone contact for any new Adverse Events (AEs) or Serious Adverse Events (SAEs).

E.1.a. Risks to Participants

E.1.a.1. Sources of Materials

The research material collected from participants includes: a) biological specimens (i.e., blood, urine, and breath alcohol samples); b) review of medical and psychiatric records; and c) self-report on medical and psychiatric history, alcohol and drug use, and current psychiatric status. The study physician will collect information regarding medical and psychiatric history. Research staff trained in phlebotomy and biological specimen processing will collect blood, urine, and breath alcohol samples. Trained research staff will conduct neuropsychological assessment, administer self-report questionnaires, and conduct semi-structured interviews.

Information regarding specimens and data collected will be recorded on research forms, which will be coded with a unique identifying number. A master list linking this unique identifying number with the participant's name will be maintained together with original copies of the consent forms in a locked file cabinet in a locked research room. Specimens and data collected during research visits will be used only for the proposed research project. Research staff working on this specific project will be the only individuals with access to this information with the following exception: if information obtained during the study indicates the possibility of danger to the participant or others, the information may be shared with clinical care providers for that participant, in order to ensure safety.

E.1.a.2. NAC Medication Risks

Adverse effects:

NAC is generally a safe and tolerable medication that is available in the oral form as a non-prescription dietary supplement in many health food stores. Its clinical use by prescription is for a variety of FDA-approved indications including acetaminophen overdose, cystic fibrosis. Such use is generally in the intravenous, nebulized liquid, or oral liquid forms and is used at much higher doses than those proposed in this project (for example as much as 40 grams per day orally for acetaminophen overdose as compared to the 2400 mg per day in the proposed study). Adverse effects using the above routes of administration at the high doses utilized have included stomatitis, nausea, vomiting, fever, rhinorrhea, drowsiness, clamminess, chest tightness, and bronchoconstriction. Clinically overt acetylcysteine induced bronchospasm occurs infrequently. Acquired sensitization to acetylcysteine has been reported rarely. Most of the following adverse effects are derived from studies employing the intravenous form of NAC, not the oral form that is to be used in the proposed project. NAC in its oral form has low toxicity and few known clinically significant adverse effects observed in doses up to 8000 mg/day (Arkury, 2007; Hoffer 2013), which covers the dose range to be used in the proposed study.

Frequency of adverse effects[170,208]:

Common

- Dermatologic

  - Pruritus: 1% - 3%
  - Rash: 4% - 5%
  - Urticaria: 6.1%
  - Flushing: 2% - 4%
- Gastrointestinal
  - Diarrhea: 2% - 7%
  - Vomiting: 9% - 12%
  - Nausea: 2% - 7%
- Cardiovascular
  - Edema: 1.2% - 1.6%
  - Hypotension: 0.1%
  - Tachycardia: 3% - 5%
- Immunologic
  - Anaphylactoid reaction: Incidence unclear
- Other
  - Angioedema: Incidence unclear

E.1.a.2.a Reproductive/Pregnancy risks:
Pregnancy: Teratogenic Effects: Pregnancy Category B:
NAC is classified as pregnancy Category B, "Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters)."

Animal studies have generally not shown teratogenic effects. They also have revealed no evidence of impaired fertility or harm to the fetus due to acetylcysteine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies may not always be predictive of human responses, this drug should be used during pregnancy only if clearly needed for clinical care. Therefore pregnant women will be excluded from the study.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when acetylcysteine is administered to a nursing woman. Therefore nursing women will be excluded from the study.

E.1.a.3. Blood Drawing (Venipuncture) Risks
Participation in the study requires participants to have their blood drawn 3 different times over the course of 8 weeks. Having blood drawn may cause pain (common), fainting/passing out (not very often), a bruise where the needle goes in (not very often), and infection at the same place (rare).

E.1.a.4. Risk to Privacy/Confidentiality
Participation in the study presents a risk to the participant of loss of privacy and confidentiality regarding research material, particularly with respect to potentially embarrassing or harmful personal health information, particularly related to mental health and alcohol and substance use. This includes detailed and sensitive information regarding alcohol and drug use, and psychiatric symptoms. For example, urine drug testing will be conducted. Potential release of information regarding drug use, in particular, could have serious implications if made known, for example legal ramifications, jeopardizing insurability or employability.

In order to ensure the safety of the participant and others, information may be shared between research staff and the clinical team only under the following circumstances: 1) If in the judgment of the study physician, the participant has a psychiatric or medical condition that requires urgent attention to protect the safety of the participant or others; and 2) If a participant has missed several study appointments, and research staff needs to verify the participant's whereabouts and/or verify the participant's safety. These above circumstances will be clearly outlined in the informed consent form, and be discussed and clarified with prospective participants at the start of the study.

E.1.a.5. Randomized risks
Participants will be assigned to a treatment program by chance, and the treatment received may prove to be less effective or to have more side effects than other available treatments.

E.1.a.6. Risk of relapse or increased alcohol use
Participants may face the risk of relapse or to increased alcohol use. This risk may be greater if they are assigned to receive placebo as compared to NAC, although the exact nature of this risk is unknown.

E.1.b. Adequacy of Protection Against Risks

E.1.b.1. Informed Consent
Participants will be educated of the risks attendant to study participation through the informed consent process.

E.1.b.2. Protection Against NAC Medication Risks
To protect against this risk, we will do the following:
a.) Protection Against Adverse Effects

1. IND: We have informed the FDA and asked for guidance regarding the possible need for an IND.
2. We will provide participants with a complete list of adverse effects and other medication risks at the time of obtaining informed consent, and we will also inform participants of the following:

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

- Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
- Chest pain
- Facial flushing or rash
- Swelling in your hands, ankles, or feet

If you notice these less serious side effects, talk with your doctor:

- Clammy skin
- Drowsiness
- Nausea or vomiting
- Sore mouth

E.1.b.2.a. Protection Against Reproductive/Pregnancy Risks
To protect against these risks, we will do the following:

1) Birth Control/ Pregnancy Assessment will be done at baseline/screening, weeks 4, 8, and 12. Any participant who becomes pregnant during participation in the study will be withdrawn. The results will be recorded on a Birth Control/Pregnancy Assessment Form.
2) In the informed consent form, participants are instructed: “You should not become pregnant while on this study because NAC may harm the fetus. Women of child bearing potential will be asked to use birth control. Acceptable methods include condom, spermicide, diaphragm, or not having sex. Pregnancy tests will be done monthly throughout your participation in the study to assure that you are not pregnant. If you become pregnant during the study, study treatment will be discontinued and one of your alternative treatment plans may be implemented. If you are practicing abstinence, you must agree to continue abstinence or use an acceptable method of contraception should sexual activity commence.

E.1.b.3. Protection Against Blood Drawing/Venipuncture risks
To protect against this risk, we will do the following:

1) Professionally trained phlebotomists at the SFVAMC Clinical laboratory will perform all phlebotomies.

E.1.b.4. Protection Against Risks to Privacy/Confidentiality
To protect against this risk, we will do the following:

1) In the informed consent form, participants are instructed: “Participation in research may involve a loss

of privacy, but information about you will be handled as confidentially as possible. If you do not already have a medical record at the VA Medical Center, San Francisco, one will be created because of your participation in this study."

2) *HIPAA regulations will be followed throughout this study.*

3) Several methods will be used to decrease the risk *of loss* of confidentiality to participants. First, all study forms will be labeled with a unique, identifying code number, and maintained in a locked cabinet. Those that contain the names of participants or other identifying information will be stored in a locked cabinet, separate from other study forms. Second, research material will not be shared between the research team and clinical staff - with the exception of information to be shared only to ensure the safety of the participant and others. Third, no names will be used in any published reports about this study. We anticipate that the above procedures will be highly effective in decreasing the likelihood of loss of privacy or confidentiality to participants in the proposed research project.

E.1.b.5. Protection Against Randomization Risks

To protect against this risk, we will do the following:

1) During the informed consent process, key personnel will explain the definition of randomization and its associated risks.
2) In the informed consent form, participants are instructed, "You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than other available treatments."

E.1.b.6. Protection Against Risk of Relapse or Increased Alcohol Use

To protect against this risk, we will do the following:

1) We will closely monitor alcohol use at each weekly visit.
2) Participants will be withdrawn from the study if, in the opinion of the PI or the DSMB, there is: sustained clinically significant worsening in the primary outcome measure of alcohol use, unacceptable adverse events judged to be related to study interventions, or any other clinically significant medical, psychiatric, or substance use related poor outcome that makes continued study participation unsafe.

E.1.b.7. Reporting Unanticipated Problems Involving Risk to Participants or Others

All unanticipated problems involving risk to participants or others, serious adverse events related to participation in the study and participant deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

E.1.c. Adverse Event Reporting

E.1.c.1. Introduction

The PI will be responsible for following adverse event reporting requirements as outlined below in the protocol. These responsibilities include reviewing the accuracy and completeness of all adverse events reported; compliance with IRB policies for reporting adverse events and serious adverse events; reporting any safety issues to the IRB; and closely monitoring research volunteers at each study visit and telephone contact for any new Adverse Events (AEs) or Serious Adverse Events (SAEs).

E.1.c.2. Adverse event definition

Adverse Events (AEs) will be collected using the definition of the UCSF IRB and International Conference on Harmonization (ICH) for Clinical Safety Data Management (ICH-E2A), according to which an adverse event is "any untoward medical occurrence in a patient or clinical investigation participant administered a pharmacological product which does not necessarily have to have a causal relationship with this treatment." An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of

diagnostic procedures including laboratory test abnormalities.

E.1.c.3. Serious adverse event definition

Research staff will immediately notify the study physician in the event of a serious adverse event (SAE). In the event of one that is life-threatening or requires hospitalization, the participant's medical status will be monitored and the decision of whether to withdraw the participant from the study will be made on an individual basis by the study physician based on severity and nature of the medical problem. For all adverse reactions that are serious, life-threatening, or require hospitalization, the principal investigator and research coordinator will notify the UCSF IRB and the Federal Drug Administration (FDA) using the standard procedures provided by each agency. An FDA adverse reaction form will be completed at that time.

E.1.d. Participant Withdrawal

Participants will be withdrawn from the study if:

- in the clinical judgment of the investigator, the participant requires acute detoxification from alcohol,
- in the clinical judgment of the investigator, the participant's clinical condition worsens substantially (for example, if weekly alcohol use increases 25% or more over baseline) and it is felt to be in the participant's best interest to obtain alternative treatment including, but not limited to, additional psychotherapy, pharmacotherapy, hospitalization, etc.
- the participant becomes pregnant. Should a participant become pregnant at any time during the study the participant will immediately discontinue study medication. Study medication will not be tapered.

E.2. DATA AND SAFETY MONITORING

E.2.a. Plan to Monitor Study Progress and Safety: The Data and Safety Monitoring Plan (DSMP)

The DSMP for this project consists of:

- a Data and Safety Monitoring Board (DSMB)
- a schedule of DSMB meetings to review study data and events
- a list of study data and event items to be reviewed by the DSMB
- procedures for communicating DSMB findings to the UCSF IRB, and other appropriate entities
- a plan for conducting and reporting interim analysis
- stopping rules
- rules for withdrawing study participants from the study interventions

Note: These elements of the DSMP are described below:

E.2.b. The Data and Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) is a group of 3 physicians who are clinicians as well as clinical researchers, and who are not study investigators. They have expertise in the areas of clinical psychiatry, clinical psychopharmacology, neurocognitive functioning, traumatic brain injury and substance use disorders. The composition of the DSMB is: Anne Richards, M.D., M.P.H., Staff Psychiatrist, SFVAMC; Steven Lieske, M.D., Staff Psychiatrist, SFVAMC; and William Wolfe, M.D., SFVAMC.

The DSMB will meet quarterly to review data reports prepared by the PI regarding the progress of the study and will monitor patient enrollment, retention, outcomes, adverse events, and other issues related to patient safety. The DSMB will make recommendations to the PI as to whether the study should continue or be modified or terminated. The DSMB can consider patient safety or other circumstances as grounds for early termination. Any member of the DSMB can ask for a meeting of the group if he/she feels that it is necessary, based upon the data.

During the course of the study, reports will be prepared and distributed to the Data and Safety Monitoring Board on a quarterly basis. In order for the Data and Safety Monitoring Board to discharge their duties for overseeing the study and the rights of the patients, they will receive analyses of the primary outcome measures and the important exploratory measures on a quarterly basis. The DSMB will receive reports of serious adverse events (SAEs) within 72 hours of their occurrence. DSMB Minutes will be prepared by the Study Coordinator within 5 working days after each quarterly DSMB meeting.

E.2.c. Research Monitor
Anne Richards, MD, MPH, is an Assistant Clinical Professor at UCSF and Staff Psychiatrist at the SFVAMC. Her clinical and research interests are in the area of traumatic stress. Dr. Richards will serve as Research Monitor. At a minimum, the research monitor: (1) may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research; (2) shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the UCSF CHR can assess the monitor's report; (3) shall have the responsibility to promptly report their observations and findings to the IRB or other designated official. As Research Monitor, Dr. Richards will review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. The medical monitor will comment on the outcomes of the event of problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The Research Monitor will also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the USAMRMC ORP HRPO.

E.2.d. Schedule of DSMB Meetings
The DSMB will meet semi-annually.

E.2.e. List of Study Data and Event Items to be Reviewed by the DSMB
Data reports prepared by the PI regarding the progress of the study will include patient enrollment, retention, analyses of the primary outcome measures (alcohol use, brain injury symptom severity, and cognitive performance) and important exploratory outcome measures (other alcohol use measures), adverse events, serious adverse events, and other items related to patient safety.

E.2.f. Procedures for Communicating DSMB Findings to Appropriate Regulatory Bodies
The PI will communicate DSMB findings in the form of copies of the minutes of each quarterly DSMB meeting, within 10 working days following each meeting. Reports will be sent to the UCSF IRB, and SFVAMC Human Research Protection Program (HRPP).

E.2.g. Stopping rules
The study will be stopped if, in the judgment of the DSMB or the PI, there are sufficient safety concerns that arise during the conduct of the study that would indicate that participants are being harmed by study interventions. Examples of such safety concerns would be:
- If, after the first 10 participants (33% of the planned enrollment) have completed their study treatment, the interim analysis reveals that more than 50% (i.e. 6 participants) have worsened to a clinically significant degree in the primary outcome measure of alcohol use from baseline to study end.
- Other events that pose unacceptable risks to participants, e.g., multiple SAEs that are judged to be related to study interventions

E.2.h. Rules for Withdrawing Study Participants from the Study Interventions
Participants will be withdrawn from the study if, in the opinion of the DSMB or the PI, there is: sustained clinically significant worsening in the primary outcome measure of alcohol use, unacceptable adverse events judged to be related to study interventions, or any other clinically significant medical, psychiatric, or substance use related poor outcome that makes continued study participation unsafe in the clinical judgment of the PI or DSMB members.

E.2.i. Rules for Breaking the Blind
The blind will be broken for an individual in the study if, in the opinion of the PI or DSMB, there is an emergent clinical need to determine whether a participant is receiving NAC or placebo.

E.3. BENEFITS TO TAKING PART IN THE STUDY
Participants may benefit from the extra physical examination, laboratory tests, and attention to and treatment

of alcohol use disorders. In the informed consent form, participants are instructed: “Taking part in this study may or may not make your health better. If you are in this study, you may benefit from the physical examinations, blood tests, and review of your symptoms. You may respond favorably to the treatment and reduce your drinking and brain injury symptoms, but there is no guarantee that this will happen. Others may benefit from the overall conclusions drawn from the results of this study.”

E.4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Hazardous and harmful drinking (HHD) is a critical issue in the treatment of people with TBI. HHD is much more common in this population and can cause much more harm than in the population at large. Existing treatments for these patients are inadequate. NAC also shows promise as a potential treatment for TBI related symptoms. Validating the efficacy of NAC could result in establishing a new treatment that effects a multi-pronged reduction in alcohol consumption, TBI severity, and an increase in cognitive performance, all target treatment areas of this highly symptomatic and understudied population.

The potential knowledge to be gained in this study is judged to be highly significant. This research seeks to expand the knowledge base regarding the effectiveness of NAC in a particularly vulnerable and difficult-to-treat population - i.e., patients with TBI who drink as hazardous and harmful levels. Because of the low risk profile of NAC and the close monitoring afforded by the study design, the level of risk for prospective participants is judged to be minimal, and therefore, is considered to be reasonable, in comparison with the potential knowledge to be gained.

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