NURA-010-16S

NCT03018704

Topiramate Treatment of Alcohol Use Disorder in African Americans

March 3, 2016

A. SPECIFIC AIMS

The current proposal aims to improve alcohol treatment in African American (AA) Veterans. AAs currently comprise 12% of the Veteran population, a percentage that is anticipated to rise steadily over the next several decades. Despite having lower rates of drinking and heavy drinking than European Americans (EAs), AAs have significantly higher rates of morbidity and mortality from a variety of alcohol-related conditions, including liver cirrhosis, accidents, and violence (1, 2).

In addition to the disparity in morbidity and mortality, there is also a lack of empirical testing of alcohol treatment medications in minority populations, including AAs. Because population differences, including genetic ones, can affect individual treatment response, there is a particular need to evaluate alcohol pharmacotherapy specifically in populations other than EAs. For instance, naltrexone, a medication that is approved for alcohol treatment by the Food and Drug Administration (FDA), has questionable efficacy in AAs (3), though it has not been evaluated fully in this population.

Although the anticonvulsant topiramate (TOP) is not approved to treat alcohol use disorder (AUD), four placebo-controlled trials conducted predominantly in EAs have shown that it substantially reduces the frequency of heavy drinking (i.e., days on which men consume five or more standard drinks and women consume four or more standard drinks) and increases the number of abstinent days (4-8). Based on these findings and the recommendation by the National Institute on Alcohol Abuse and Alcoholism that TOP be used routinely to treat alcohol dependence, the medication is increasingly prescribed "off-label" for alcohol treatment (e.g., in the VA healthcare system, where growth in prescriptions for alcohol treatment has been rapid) (9). However, like naltrexone, TOP has been evaluated almost exclusively in EAs, with a virtual absence of such studies in AAs or other minority groups.

Of relevance to the use of TOP in the treatment of Veterans with AUD, we found that the medication is efficacious only in EAs within a specific genotype group, i.e., individuals homozygous for the C allele of rs2832407, a polymorphism in the *GRIK1* gene, which encodes the GluK1 subunit of the kainate receptor, a glutamate receptor subtype (7). Importantly, rs2832407 allele frequency differs substantially among populations: the C allele is the major allele at this locus in EAs (frequency = ~0.65), but the minor allele in AAs (frequency = ~0.18). This pharmacogenetic effect persisted for 6 months from the end of active treatment (10). Thus, in addition to examining the use of TOP to reduce heavy drinking in AAs, including the persistence of treatment effects, the current proposal will explore the effects of population genetic differences on the efficacy of TOP. We propose to conduct a prospective, 12-week, parallel-group, placebo-controlled study of the efficacy and tolerability of TOP 200 mg/day in a sample of 160 heavy-drinking AA Veterans with DSM-5 AUD.

The proposal is innovative in that it: 1) provides a well-powered test of the medication's efficacy in AAs with AUD, an understudied and underserved population for which no such data currently exist; 2) includes Veterans whose goal is either to reduce drinking or become abstinent, which includes a large proportion of the AA Veteran population that could benefit from alcohol treatment; 3) uses a 200-mg/day dosage of TOP, which is better tolerated than the 300-mg/day dosage used in the largest prior studies; 4) examines the persistence of treatment effects for six months post-treatment; 4) explores the pharmacogenetics of TOP treatment in AAs, for whom precision medicine efforts are rare. To do this, we will leverage findings from the Million Veteran Program (MVP), for which genomewide association (GWAS) data will be available for more than 300,000 Veterans, and apply it to the present sample to explore genetic moderation of TOP's effects. If the MVP data are not available, we will use data from our completed GWAS of alcohol dependence for this purpose (11).

Specific Aim 1. To test the efficacy of topiramate (TOP) 200 mg/day in reducing the frequency of heavy drinking and increasing abstinent days in African-American (AA) patients with alcohol use disorder (AUD). We hypothesize that, as in EAs, AA Veterans receiving TOP will report fewer heavy drinking days (HDDs) and more abstinent days than those receiving placebo.

Specific Aim 2. To explore the moderating effect of variation in the *GRIK1* and *GRIK2* genes on TOP's efficacy in reducing heavy drinking and increasing abstinent days. We will explore the moderating effects of single nucleotide polymorphisms (SNPs) in *GRIK1* and *GRIK2*, which encode kainate subunits. Topiramate's effects are most potent and selective for kainate receptors containing these subunits. We will select SNPs for testing based on association analyses for sustained heavy drinking that are being conducted in a beta test project of the MVP (Kranzler, PI at CMCVAMC) or from a GWAS that we completed in a sample of 3,318 AAs (11).

Specific Aim 3. To examine the persistence of TOP treatment effects during a six-month post-treatment follow-up period. We hypothesize that, in a pharmacogenetically responsive subgroup, TOP's effects on heavy drinking and abstinent days will persist during the follow-up period.

B. BACKGROUND AND SIGNIFICANCE

The 2005 National Survey on Drug Use and Health showed that Veterans have a rate of heavy drinking (defined as consuming 5 or more drinks on an occasion at least 5 times in the preceding 30 days) of 7.5%. This was higher than community dwelling non-veterans who were sampled to match for age, gender, and geography (6.5%) (12). The 2014 National Survey on Drug Use and Health showed that 81.7% of African Americans (AAs) 18 years or older reported lifetime use of alcohol and 48.6 drank during the preceding 30 days, with 23.9% reporting binge drinking (i.e., 5 or more drinks on a single occasion at least once in the preceding 30 days) and 5.1% reported heavy drinking (13). This compares with 91.8% of European Americans (EAs) who reported lifetime drinking and 61.6% that reported drinking, 25% binge drinking, and 7.6% heavy drinking during the preceding 30 days. Despite the fact that AAs drink less frequently and not as heavily as EAs, AAs have significantly higher rates of mortality from alcohol-related conditions, including hepatic cirrhosis, accidents, and violence than EAs (1, 2). Further, alcohol treatment research focused on the specific needs of AAs is lacking, despite the fact that 42 million people in the U.S. (13.2% of the total U.S. population) is of African ancestry. Thus, there is a pressing need to identify better approaches to treat heavy drinking in AAs. This need appears to be particularly great in the Veterans Affairs Healthcare System (VAHS). Recently, Williams et al. examined racial/ethnic differences in clinically recognized AUD in the VAHS. They found that, among nearly 5 million eligible patients, 17.4% were AA, 6.5% were Hispanic, and 76.1% were EA (14). The overall prevalence of clinically recognized AUD was 6.5% and was greatest among AAs (9.8%), followed by Hispanics (7.1%), and it was lowest among EAs (5.7%), a highly significant difference ($p < 0.001$). The pattern generally held for men, regardless of age group, though among women, the prevalence of AUD was generally lowest among Hispanics and highest among AA patients. We propose to evaluate the effects of topiramate (TOP), a medication that appears to be the most efficacious in treating alcohol use disorder (AUD) (4), in AAs, the predominant minority population in the VAHS.

The VA has perhaps the most robust specialty addiction program of all hospital systems. Referral to these programs represents the standard of care for patients identified with AUD. An important consideration in the dissemination of treatments is their acceptability to clinicians and the healthcare context in which they are to be applied. In the VAHS, there has been a systematic effort to identify at-risk or harmful drinkers using the first three questions of the Alcohol Use Disorders Identification Test (i.e., the AUDIT-C) (15). The effort aims to promote the use of brief interventions and referrals for AUD specialty care. However, only 3.9% of veterans identified as needing an intervention for alcohol dependence (based on an AUDIT-C score of $\geq$8) received SUD specialty care in the year following screening (16). Consistent with the notion that focused efforts can eliminate healthcare disparities, AA veterans were significantly more likely than EA Veterans to be identified (14) and receive treatment after identification (17). Similarly, in a cross-sectional analysis of data from >250,000 individuals in the VHA, among individuals who acknowledged drinking, AA patients (odds ratio=1.65) and Hispanics (odds ratio=1.56) were more likely than EA patients to receive alcohol-related advice (18). These findings speak highly of the VHA's efforts to identify individuals who need an alcohol intervention, which have helped to identify and treat both AAs and Hispanics with AUDs. This is in contrast to the findings outside of the VA, where minority individuals, especially those at the highest levels of alcohol dependence severity, underuse alcohol treatment services relative to non-Hispanic EAs (19).

B.1. Medications to Treat Alcohol Dependence: The VA/DOD Substance abuse treatment guidelines recommend that pharmacotherapy be offered to all Veterans with a moderate-to-severe AUD unless there are medical contraindications. This is also the VA policy outlined in the Uniform Services Handbook for Mental Health Services. The VA/DOD guidelines recommend the use of the three medications approved by the Food and Drug Administration (FDA) to treat AUD: disulfiram, naltrexone (both oral and long-acting formulations), and acamprosate. In addition to these three medications, the guidelines explicitly call for the use of topiramate.

The recommendations are based on evidence supporting the use of all of these medications to treat AUD. However, the efficacy of disulfiram has been questioned (20) and findings regarding acamprosate are inconsistent outside of Europe (21). Oral naltrexone has a small, but statistically reliable effect in reducing heavy drinking (22). The efficacy of long-acting naltrexone to enhance medication adherence in alcohol dependence was demonstrated in a single placebo-controlled clinical trial, but the findings have not yet been replicated (23). As previously mentioned, TOP is a promising treatment for AUD. Harris et al. found that in FY 2009, only 4.7% Veterans with current alcohol dependence were prescribed naltrexone, acamprosate, or disulfiram, the three FDA-approved medications (24). This rate increased to 6.5% when TOP was included among the alcohol treatment medications. AA Veterans also appear to use naltrexone at lower rates than EAs

(25). This is consistent with a literature on treatment choices, which shows that AAs prefer not to use medications when treated for depression (26, 27).

B.1.a. Results of studies of medications to reduce drinking in AAs: A secondary analysis of findings from the Combine Trial, a large, 16-week, multi-center, placebo-controlled comparison of naltrexone and acamprosate, showed no significant benefit of naltrexone treatment among AAs (3). Specifically, there was no difference on percent days abstinent, time to first heavy drinking day, and global clinical outcome in AAs treated with naltrexone (n=51) from those assigned to placebo (n=49), controlling both for acamprosate treatment and the concomitant behavioral intervention. Because the samples for the comparison were small, this finding may reflect Type II error. However, negative findings for naltrexone were also obtained in a human laboratory study conducted by our group, in which 43 non-alcohol-dependent AA social drinkers participated in four separate alcohol challenge sessions, each separated by at least 10 days (28). During each session, after double-blind pretreatment with either naltrexone (50 mg/day) or placebo, subjects consumed alcohol or sham drinks. There was an effect of alcohol on subjective reports, consistent with prior effects in a human laboratory setting. However, naltrexone pretreatment did not influence these effects. There are no other controlled trials in the literature, of which we are aware, that evaluated medication effects on drinking in AAs. Thus, adequately powered studies are needed to evaluate medications for treating AUDs in AAs, a medically underserved population in which treatment research is limited.

B.1.b. Topiramate for Treating AUD: Topiramate is approved by the FDA to treat seizure disorder and prevent migraine and (in combination with phentermine) for weight loss. It is associated with mild-to-moderate adverse effects and is best tolerated when initiated at a low dosage and gradually increased over a period of weeks. Two randomized controlled trials of TOP 300 mg/day showed that it has a medium-sized effect in reducing heavy drinking and promoting abstinent days in patients with alcohol dependence (5, 6). In the first study, a 12-week study in 150 subjects, the medication was well tolerated and TOP-treated subjects had a significantly greater reduction in the percentage of heavy drinking days and a greater increase in abstinent days than those receiving placebo (5). In this study, the TOP group separated significantly from placebo on drinking outcomes after the first month of treatment. In the second study, a 14-week, double-blind, placebo-controlled, multicenter trial in 371 subjects with AD, TOP was significantly more efficacious than placebo at reducing the percentage of heavy drinking days and increasing the number of abstinent days(6). However, in contrast to the previous trial, in this study, TOP treatment was associated with a significantly higher rate of early discontinuation from treatment than placebo, suggesting that a lower dosage of the medication could be clinically advantageous. Miranda et al. randomly assigned 61 non-treatment-seeking heavy drinkers to receive treatment with TOP 200 mg/day, TOP 300 mg/day, or placebo (8). The medication was titrated to the target dosage over a 32-day period and maintained there for one week. During the titration period, the frequency of heavy drinking was significantly lower in both TOP groups than with placebo, supporting the potential utility of using the 200-mg/day dosage of TOP.

Open-label trials of TOP conducted in Spain (29) and in Greece (30) also provided evidence of the utility of TOP in individuals of European descent. However, a placebo-controlled study conducted in Thailand failed to show a significant advantage of TOP in reducing drinking in that population (31). The interpretation of the findings from that study is limited by the low rate of study completion (53% in the TOP group and 47% in the placebo group) resulting in a large amount of missing data. Further, there was no evaluation of adherence to the prescribed regimen. A meta-analysis of 7 randomized controlled trials (a total of 1,125 participants) compared topiramate to placebo for treating AUD(4). The largest effect for topiramate was found on the following outcomes: abstinence ($g = 0.468$, $p < 0.01$), heavy drinking ($g = 0.406$, $p < 0.01$), the liver enzyme GGT ($g = 0.324$, $p = 0.02$), and craving for alcohol ($g = 0.312$, $p = 0.07$). The authors concluded that the efficacy was greater magnitude than that of either naltrexone or acamprosate. However, despite a growing literature on the use of TOP for treating AUD, there are no published studies that have enrolled a substantial number of African-ancestry patients, so that our knowledge of the potential utility of TOP for treating AUD in AAs is non-existent.

We completed a 12-week, placebo-controlled trial of the efficacy of TOP 200 mg/day. The dosage in that study was chosen to be more tolerable than the 300-mg/day dosage used in most of the prior studies. The study enrolled 138 heavy drinkers [62.3% male, 88.4% European American (EA)] whose goal was to reduce their drinking (7). Patients were randomly assigned to receive 12 weeks of treatment with TOP (N=67, 48.6%) or matching placebo (N=71, 51.4%), together with medical management. During the 90-day pre-treatment period, patients in both groups were abstinent ~1 day/wk and drank heavily (men: $\geq$ 5 standard drinks; women: $\geq$ 4 standard drinks) on ~5 days/week. Fifty-six TOP patients (83.6%) and 61 placebo patients (85.9%) completed the 12-week treatment period ($p=0.70$). There was a main effect of medication group ($p<0.001$) and

an interaction of medication group with treatment week ($p<0.0001$), such that TOP patients had fewer heavy drinking days and decreased the number of heavy drinking days/week more rapidly than placebo patients (see Fig. 1 below). During week 12, the odds that the TOP group would have at least one heavy drinking day was 0.188 (95%CI=0.137-0.595) that of the placebo group ($p<0.001$). There was also a main effect of medication group on abstinent days ($p=0.032$) and an interaction with treatment week ($p=0.013$), such that TOP patients had more abstinent days and increased the number of abstinent days/week more rapidly than the placebo group. During week 12, the odds of an abstinent day in the TOP group was 2.57 (95%CI=1.13-5.84) times that of the placebo group. These findings were accompanied by significantly greater reductions in gamma-glutamyltranspeptidase (GGTP), a liver enzyme that is elevated by heavy drinking, and scores on the Short Index of Problems (SIP), a measure of alcohol-related problems, in TOP patients compared with those receiving placebo (32). These findings help to validate the self-reported drinking reductions seen in the TOP group.

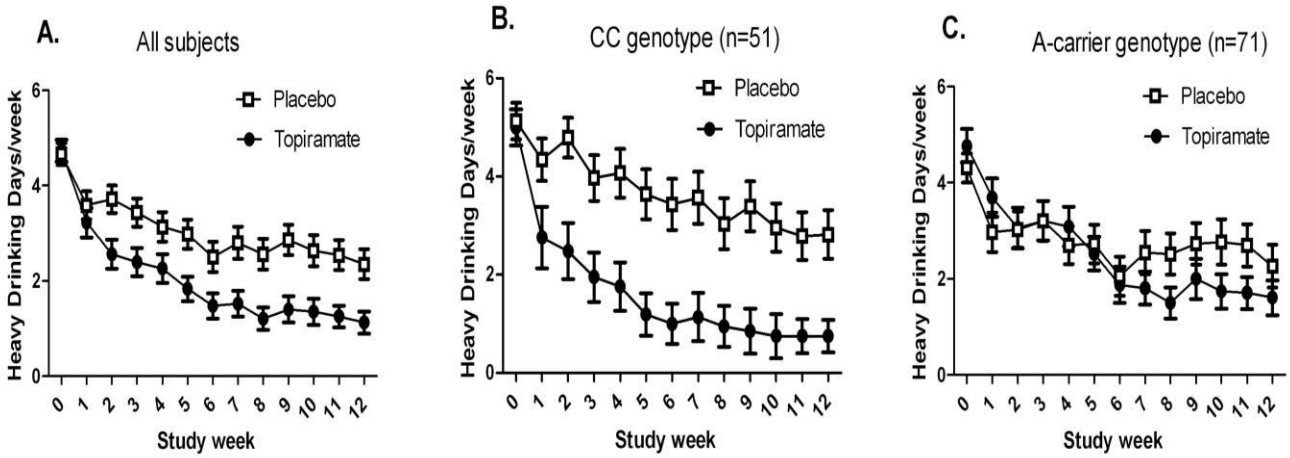

Figure 1. Heavy drinking days per week during treatment. A. All subjects (n=138); B. EA rs2832407*C-allele homozygotes (n=51); C. EA rs2832407*A-allele carriers (n=71).

Despite TOP's ability to reduce heavy drinking, because it has multiple pharmacological actions it can cause adverse effects that limit its clinical utility. To evaluate both the risks and benefits of TOP in the treatment of AUD, we re-analyzed data from our completed trial (7). To put the results in perspective, the median NNT for widely used medications to treat major depression is 7 for selective serotonin reuptake inhibitors and 9 for tricyclic antidepressants (33). In the treatment of AUD, the median NNT (unadjusted for adverse events) is 9 for both naltrexone and acamprosate (20, 21). In our analysis the NNT for TOP represents the number of patients that had to be treated to prevent any heavy drinking during the last month of treatment compared to placebo (34). We adjusted the NNT based on adverse events of moderate or greater severity, such that NNT_{AE} is the NNT at which there were no additional adverse events. Thus, NNT_{AE} for TOP combines both its beneficial and adverse effects in a single measure. We found that, overall, the NNT for topiramate was 5.29 and the NNT_{AE} was 7.52. Because of our findings regarding the moderating effect of rs2832407 genotype, we repeated the analysis using genotype, which required that we limit it to the EA subsample (n=122). Among EAs with the rs2832407*CC genotype, the NNT was 2.28 and it increased to 2.63 when adjusted for moderate or greater adverse events. In contrast, for rs2832407*A-allele carriers, the NNT was 180.00 and the adjusted NNT was 322.16. <u>These findings underscore the robust treatment effect of TOP, which overall was comparable to that seen for SSRI antidepressants in the treatment of depression, but was much greater in individuals with the rs2832407*CC genotype, even when adjusted for adverse events.</u>

To evaluate the persistence of TOP's effects, we re-interviewed patients from the completed trial 3 and 6 months after the end of the 12-week treatment (10). As was true during treatment, where we obtained 92.4% of drinking data, a high percentage of data was also obtained at the 3- and 6-month follow-up visits: 89.1% and 85.5% respectively. We examined 4 outcomes over time both in the overall sample and in the EA subsample: percent heavy drinking days, percent days abstinent, serum GGTP concentration, and SIP score. In the full sample, the lower percent heavy drinking days and higher percent days abstinent seen with TOP treatment were no longer significant during follow-up (see Figure 1A below). Nonetheless, the TOP-treated patients had lower alcohol-related problem scores during treatment and both follow-up periods (data not shown). Further, in the EA subsample, the greater reduction in percent heavy drinking days seen during treatment in rs2832407*C-allele homozygotes persisted throughout follow-up (Figure 1B), with no significant effects in A-

allele carriers (Figure 1C). Changes in GGTP concentration were consistent with TOP's effects on heavy drinking, but did not reach statistical significance.

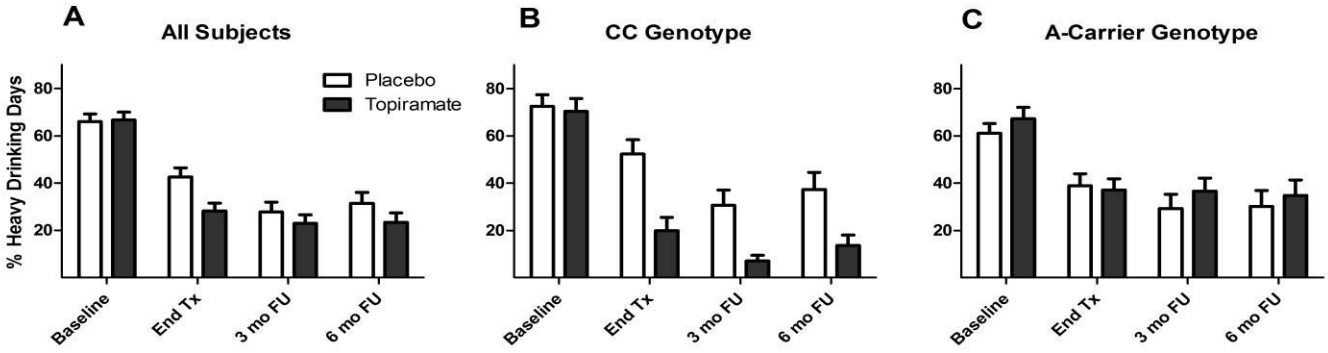

Figure 2. Heavy drinking days per week across treatment and follow-up periods. A. All subjects (n=138); B. EA rs2832407*C-allele homozygotes (n=51); C. EA rs2832407*A-allele carriers (n=71).

Analysis of drinking in the subgroup of AA patients in the study (N=12) was not informative, as the sample size was too small to draw meaningful conclusions regarding the efficacy of TOP in AAs. Importantly, though, the medication was well tolerated by these patients and a high proportion (N=11, 92%) completed the 12-week treatment, both of which support the feasibility of the study proposed here. Although we did not over sample AAs to permit an analysis of TOP's efficacy in this population, given the clear evidence of efficacy of the medication seen in EAs, a trial of TOP in AAs is warranted. Information on the feasibility of recruiting an adequate sample of AA patients for the study proposed here is presented below (section **D.1.d**).

B.1.a.1. Pharmacology of Topiramate: TOP is a sulfate-substituted monosaccharide with multiple pharmacological effects. It facilitates GABAergic function by interacting with a non-benzodiazepine site on the $GABA_A$ receptor (35), antagonizes glutamate activity at AMPA and kainate receptors (36, 37), blocks voltage-dependent Na^+ and L-type voltage-gated Ca^{++} channels, inhibits carbonic anhydrase, and enhances K^+ conductance (38).

B.1.a.2. Pharmacogenetics of Topiramate: Kainate receptors are tetrameric assemblies that respond to glutamate. TOP's effects on AMPA/kainate receptors are most potent and selective for those containing the GluK1 and GluK2 kainate subunits (encoded by *GRIK1 and GRIK2*, respectively) (39). To identify a single nucleotide polymorphism (SNP) moderator of the alcohol treatment effects of TOP, we examined the association of *GRIK1* to alcohol dependence (40). Of 7 SNPs examined, the C allele of a SNP (rs2832407) in intron 9 was significantly associated to alcohol dependence, controlling for multiple comparisons. Following presentation of these findings, Ray et al. examined the moderating effect of rs2832407 on TOP treatment outcome in 51 individuals from a placebo-controlled study of TOP in heavy drinkers (41). They found that carriers of the A allele reported more severe TOP-induced adverse effects. As described above, in our TOP study (7), we found that rs2832407 genotype (CC vs. A-allele carrier) interacted significantly with medication group (p=0.001), such that in the CC genotype group (41.8% of the total EA sample), TOP-treated patients reduced their heavy drinking days more than placebo patients (p<0.001). There was no such effect in the A-allele carrier group (p=0.70; 58.2%).

B.2. Innovation: Our proposed study is innovative in five important ways: 1) it is the first study of TOP that will enroll a sample large enough to test the medication's efficacy in AAs, an understudied and medically underserved segment of the US population; 2) it will include Veterans whose goal is either to reduce drinking or to become abstinent, which will support the study's external validity, as it will apply to a large proportion of the AA Veteran population that could benefit from alcohol treatment; 3) it will use a lower dosage of TOP than was used in the largest studies of the medication, which we have shown in EAs to enhance tolerability and treatment retention; 4) it will examine the durability of treatment effects in a six-month post-treatment follow-up, which will help to define the appropriate duration of therapy; and 5) it will explore the utility of a precision medicine (i.e., pharmacogenetic) approach to the use of TOP in AAs that will be informed by the Million Veteran Program, a major initiative in precision medicine that is being supported by the VAHS. This will be accomplished by focusing on *GRIK1*, a polymorphism of which (rs2832407) moderated the response to TOP in EAs, and *GRIK2*, a gene encoding another kainate subunit implicated in TOP's effects, in an effort to identify a genetic moderator of TOP response in AAs. We note that rs2832407 is a marker polymorphism (i.e., a biomarker) and does not appear to be functional. It may be in linkage disequilibrium (i.e., correlated) with an

as-yet unidentified functional polymorphism in *GRIK1,* or it may have a regulatory effect that has not yet been demonstrated. Because allele frequencies differ widely by population and because populations differ in their genetic backgrounds and they may have differing epistasis, it is not feasible to use rs2832407 to identify who is most likely to respond to TOP for the treatment of AUD in AAs. It is exemplary of relevant population genetic phenomena that the major (C) allele of this SNP in EAs (frequency = 0.65, with C-allele homozygotes representing about 42.4% of the EA population) is the minor allele in AAs (frequency= 0.18, with C-allele homozygotes representing only about 3.2% of the AA population). This necessitates an effort to identify another SNP in either *GRIK1* or *GRIK2* that, in AAs, serves as a biomarker in a manner function similar to that served by rs2832407 in EAs. The MVP funding recently awarded to Dr. Kranzler at the CMCVAMC to conduct genomewide association analyses for a phenotype of sustained heavy drinking jointly with investigators at the West Haven VAMC, provides an ideal opportunity to leverage this important project to inform the personalized treatment of AUD in AAs. However, we recognize that MVP data may not be available for this purpose in time for these analyses. In that event, we will use data from our GWAS in 3,318 AA subjects (11).

C. PRELIMINARY STUDIES

C.1. Preliminary Studies: To date, we have published several manuscripts from our trials of TOP treatment for heavy drinkers (6, 7, 10). In addition to this work, Drs. Oslin and Kranzler have conducted multiple clinical and human laboratory studies and published extensively on the pharmacotherapy and pharmacogenetics of AUD and on the genetics of alcohol and drug dependence (11, 42-44). That experience has informed the design of the present study and will ensure the effective execution of the research plan.

C.1.a. Prevalence of rs2832407 alleles in substance dependent and control subjects. We genotyped rs2832407 in a sample of 8,051 subjects from genetic studies of alcohol and drug dependence funded by NIAAA and NIDA. The sample was comprised largely of EA and AA subjects, with the frequency of the rs2832407*C allele overall was 65.1% in EAs but 17.9% in AAs. This underscores the limited potential for *clinical* utility of rs2832407 as a moderator of TOP's effects in AAs because of the low frequency of the CC genotype in that population (i.e., only 3.2% compared with 42.4% in EAs). Importantly, the SNP is presumably only a marker, rather than a functional polymorphism. Thus, its lack of utility in AAs as a marker of likely TOP treatment response is not surprising, as allele frequencies are known to vary widely by population. These findings underscore the need to identify population-specific genetic moderators of TOP response, which is an exploratory aim of this proposal.

C.1.b. Million Veteran Program (MVP) Beta Test. The MVP is a national, voluntary research program funded entirely by the Department of Veterans Affairs Office of Research & Development. The goal of MVP is to recruit 1 million Veterans receiving their care in the VA Healthcare System to study how genetic variation affects health. When completed, MVP will be one of the world's largest medical databases (it has already enrolled >450,000 Veterans). In response to a request for proposals for beta test projects on the first 300,000 genotyped samples, a collaborative group of investigators from West Haven VAMC (led by Dr. Amy Justice) and the Crescenz VAMC in Philadelphia (led by Dr. Kranzler) submitted a proposal to use data from the VA's Computerized Patient Record System combined with phenotypic data collected as part of the MVP assessment to conduct genomewide association testing for sustained heavy drinking, using longitudinal data from the AUDIT-C. The AUDIT-C is a self-reported screening test consisting of the first three questions of the 10-item Alcohol Use Disorders Identification (15). It has been a required annual screening test in VA primary care since 2005. It has been shown to have high sensitivity and specificity for alcohol use disorders (16). We recently received funding from the MVP to conduct analyses using data from the first 300,000 Veterans genotyped in this project. We plan to use those data to identify variants in *GRIK1* and *GRIK2* that in AAs are associated with sustained heavy drinking and thus may be moderators of the response to TOP in our sample. This would parallel our prior effort in EAs, in which we identified rs2832407, which predicted the response to TOP in a sample of EAs, using association analyses for alcohol dependence. We plan to use a similar strategy here: namely, we will examine variants that are most strongly associated with sustained heavy drinking as genetic moderators of the TOP treatment response in AAs. We also recognize that the MVP data may not be available for this purpose when we are ready to conduct our pharmacogenetic analyses. In that case, we will use data from a sample of 3,318 AAs (including nearly 2,000 individuals with alcohol dependence) who we genotyped on the Illumina Human 1 M array containing 1,069,796 total SNPs (11).

C.1.c. Recruitment for alcohol treatment trials at the CPL Michael J Crescenz Veterans Affairs Medical Center (CMCVAMC). It is important to recognize that this project is particularly relevant to the CMCVAMC, as approximately 40% of the patients served by the CMCVAMC are AAs. Further, recruitment at CMCVAMC is facilitated by a unique process that allows for the systematic assessment of all patients seeking

mental health care. The Behavioral Health Laboratory (BHL), a central element of the VISN 4 Mental Illness Research, Education, and Clinical Center (MIRECC) at the CMCVAMC, is a clinical service for primary care at the that also provides a referral service to research studies. All new patients with psychiatric symptoms or regular substance use are referred to the BHL for an initial structured evaluation. Patients who are interested and potentially eligible to participate in research are referred by the BHL to an appropriate study. Over the past three years, a total of 425 AA patients between 18 and 70 years old were assessed and found to meet criteria for AUD. In addition, the addiction treatment clinic of the CMCVAMC treats about 2,000 patients per year, of which about 50% are AA. Assuming a rate of recruitment of 35%, which is consistent with our experience recruiting research participants through the BHL, we anticipate being able to enroll >4 patients per month to participate in the proposed study.

C.1.d. Treatment preferences. In a prior VA study of the treatment of AUD at the CMCVAMC, data from which are not yet published, we examined preferences for different treatment options among patients (n=183) who were not actively in treatment. The questionnaire on preferences asked subjects to rate the degree of confidence they had in the treatment that was being offered to them and their preference for that treatment. Results showed that AAs had a greater preference for self-help groups than EAs (27% vs. 17%, $p<0.01$), but there was no difference in their confidence in self-help groups (35% of both groups indicated that self-help groups would be effective). AAs also had a greater preference for intensive outpatient treatment (28 vs. 7%, $p<0.01$) and greater confidence that the treatment would be effective (40% vs. 16%, $p<0.001$) than EAs. Preference for naltrexone (44%) and confidence in its effectiveness (44%) was high for both populations. These data suggest that Veterans at CMCVAMC have a strong preference for novel treatments, including pharmacotherapy and, unlike what has been reported for antidepressant treatment (26), we saw no difference between AAs and EAs in the preference for using medications to treat AUD.

C.1.e. Discussion. Drs. Kranzler and Oslin each have more than 20 years of experience in the conduct of trials such as the one proposed here and in the recruitment and treatment of AAs with AUD. In addition to clinical trials, both investigators have conducted studies of allelic variation contributing to the risk of alcohol dependence and genetic moderators of pharmacological treatments for AUD. Particularly relevant to this project are findings by Kranzler et al. showing a robust treatment effect of TOP, with evidence of moderation of the treatment effect EAs by rs2832407, a SNP in the *GRIK1* gene (7). Kranzler et al. also found that the effects of TOP on heavy drinking in the CC genotype group persisted throughout a six-month post-treatment period (10). These findings led us to pose the key questions to be addressed in this project: namely, whether TOP is efficacious in AAs, a largely understudied and medically underserved segment of the US population, and if so, the extent to which TOP's effects persist beyond the active treatment period. Further, the identification of genetic variation in AAs that moderates the treatment response is a key question that stems logically from the pharmacogenetic findings of Kranzler et al. (7). However, because of the large difference in rs2832407 allele frequencies between EAs and AAs, an examination of the moderating effects of the response to TOP in AAs that goes beyond that SNP is needed to address an important question that is relevant to precision medicine: namely, can genetic variants be used to identify, in advance, which AA patients are likely to experience the greatest reductions in heavy drinking and potentially the fewest adverse effects from TOP treatment. Thus, potential genetic moderators identified through analyses of genomewide association testing (conducted by the MVP or using data that we obtained) will be explored in the AA study sample.

D. RESEARCH DESIGN AND METHODS

D.1. Overview: The proposed study, which will be registered on clinicaltrials.gov, is a two-arm, 12-week, parallel-groups comparison of TOP and placebo in reducing the frequency of heavy drinking days and increasing the frequency of abstinent days in 160 AA Veterans with AUD. We will enroll Veterans whose goal is either to reduce drinking to safe levels or stop drinking. At each visit, all patients will receive Medical Management, a manualized form of supportive care that encourages them to achieve their drinking goal (MM) (45). Random assignment to treatment group and double-blind conditions will be maintained throughout the study. Raters will be trained in the reliable use of all assessments. We will use serum %dCDT to validate patient reports of drinking.

D.2. Patients: One hundred-sixty AA men and women will be recruited using a variety of methods including clinical referrals, IRB-approved advertisements, and referral from the BHL program at the CMCVAMC. We will also obtain IRB approval to identify prospective patients using the electronic health record.

D.2.a. Inclusion Criteria: a) self-identification as AA, which has been shown to be highly correlated with genetic ancestry (in 3,636 subjects of varying race/ethnicity, only 5 (0.14%) showed genetic cluster

membership different from their self-identified race/ethnicity (46)); b) age 18 to 70 years, inclusive; c) average weekly ethanol consumption of ≥24 standard drinks for men or ≥18 standard drinks for women, with a weekly average of ≥ 2 heavy drinking days (men: ≥ 5 standard drinks; women: ≥ 4 standard drinks) during the month before screening; d) a current diagnosis of moderate or severe AUD (i.e., meeting at least 4 of 11 DSM-5 AUD criteria); e)expressed goal to reduce or stop drinking; f) able to read English at the 8th grade or higher level and without gross cognitive impairment; g) willing to nominate an individual who will know the patient's whereabouts to facilitate follow up during the study; h) women of child-bearing potential (i.e., who have not had a hysterectomy, bilateral oophorectomy, tubal ligation or are less than two years postmenopausal), must be non-lactating, practicing a reliable method of birth control, and have a negative serum pregnancy test prior to initiation of treatment; and i) willing to provide signed, informed consent to participate in the study.

D.2.b. Exclusion Criteria: a) a current, clinically significant physical disease or abnormality on the basis of medical history, physical examination, or routine laboratory evaluation, including direct bilirubin elevations of >110% or a transaminase elevation >300% of normal; b) history of nephrolithiasis; c) history of glaucoma; d) current serious psychiatric illness (i.e., schizophrenia, bipolar disorder, severe or psychotic major depression, borderline or antisocial personality disorder, eating disorder, or imminent suicide or violence risk); e) current moderate-to-severe alcohol withdrawal requiring pharmacological treatment (see Section **D.4.a.** regarding alcohol detoxification); f) current DSM-5 diagnosis of drug use disorder (other than nicotine or cannabis); g) a history of hypersensitivity to TOP; h) current regular treatment with a psychotropic medication, including medications that, when combined with alcohol, present a risk of overdose (e.g., chronic opioid use) (of note we will allow subjects to discontinue medications that have no demonstrated therapeutic effect in order to enroll); i) current treatment with TOP or a medication approved for AUD; j) considered to be unsuitable candidates for receipt of an investigational drug.

D.2.c. Temporal Sequence of Study Procedures: Following an introduction to the study and review of the clinical chart, prospective patients will be scheduled for an in-person visit, where informed consent will be obtained and patients will undergo an interview to assess inclusion and exclusion criteria. Excluded Veterans will be referred for appropriate treatment based upon consultation with the study physician.

D.3. Study Periods:

D.3.a. Visit 1 (Baseline assessment): At this first visit, patients will have the study procedures explained to them, be given an opportunity to ask questions and be asked to provide informed consent. They will be required to have a zero breathalyzer reading to ensure that they are capable of giving informed consent. Patients will have their reading ability evaluated with the Slosson Oral Reading Test (47). The physician or nurse practitioner will obtain a medical and psychiatric history and will administer the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) (48). If the CIWA-Ar score exceeds 10, the patient will be offered ambulatory medical detoxification prior to randomization. Patients with alcohol withdrawal deemed too severe to treat on an ambulatory basis (e.g., CIWA-Ar score > 20, presence of a history of severe or complicated withdrawal) will be referred for inpatient detoxification. Blood and urine samples will be taken for routine clinical laboratory evaluations (including GGTP), drug screening, pregnancy testing, and DNA extraction. If necessary, the baseline assessment can be conducted over several visits to complete all assessments.

Table 1: Dosing Schedule for Topiramate

Wk	AM Dose	PM Dose	Total Daily Dose
1	0 mg	25-mg cap	25 mg
2	0 mg	50-mg cap	50 mg
3	25-mg cap	50-mg cap	75 mg
4	50-mg cap	50-mg cap	100 mg
5	50-mg cap	100-mg cap	150 mg
6-12	100-mg cap	100-mg cap	200 mg

D.3.c. Visits 2-11 (Treatment and End-of-Treatment Visits): Patients will receive the first counseling session and study medication immediately following the randomization visit (i.e., in visit 2). The dosage of TOP or matching placebo will be gradually increased over 6 weeks (Table 1). In the multicenter trial of TOP (6), TOP 300 mg/day was associated with greater attrition than placebo. In contrast, in our TOP trial (7), patients received a maximal daily dosage of 200 mg of TOP, which was efficacious and well tolerated (84.9% of patients completed the study, with Timeline Follow-back data available on an average of 92.4% of days). We will use the 200-mg maximal dosage here and a block randomization scheme to balance patient assignment on treatment goal (reduced drinking vs. abstinence).

During the 12-week treatment period, patients will return to the clinic weekly for 6 weeks and biweekly for 6 weeks (i.e., a total of 9 sessions). At each visit, we will measure their breath alcohol level (BAL), weight, and vital signs. They will complete questionnaires and receive MM counseling (see below).

At the end of treatment, a research coordinator will conduct a repeat research assessment. Measurement of serum %dCDT will be used to assess the validity of self-reported drinking. To facilitate intent-to-treat (ITT) analyses, all patients will be asked to complete all scheduled assessments and an end-of-treatment evaluation, for which they will be paid $50. Patients will also be compensated $50 for each of two post-treatment follow-up visits. Patients will receive $10/visit for transportation costs for each visit after the screening visit (i.e., $120 for all 12 visits, including post-treatment follow-up visits). They will also be paid $5 for each visit at which they return the medication container (n=8 visits). The total compensation available to patients will be $310 for full participation.

D.4. Study Treatments: Throughout the study, we will maintain double-blind conditions regarding medication condition. MM will be delivered by a nurse experienced in its use during a TOP trial. The physician will meet with the patient at the beginning of treatment (and as needed thereafter) and will meet with the nurse weekly to discuss clinical management. The nurse practitioner or study physician will order and dispense study medications.

D.4.a. Medication Condition: The maximal dosage of TOP to be used in the present study is 200 mg/day in two divided doses and a six-week titration period based on prior evidence of efficacy and tolerability (7,(8). The nurse, in consultation with the study physician, will guide patients as they increase their medication dosage. TOP will be purchased commercially and formulated in opaque capsules by the Investigational Drug Service (IDS). Placebo capsules will be formulated to match the active medication.

D.4.b. Counseling. At each treatment visit, all patients will receive brief counseling using Medical Management (MM), a medically oriented intervention developed for the COMBINE Study (45). It supports the use of pharmacotherapy and maximizes medication adherence in the treatment of AUD. MM is feasible in most medical settings, but unlikely to obscure a medication effect. We modified the MM manual to include a goal of sensible drinking for use in our completed TOP study, where it was well received (7). In MM, the clinician highlights the patient's symptoms of AUD and his or her need for treatment, advising the patient to reduce or stop drinking (consistent with his/her goal), providing a rationale to take the medication, and emphasizing the importance of daily medication adherence. For patients who choose a goal of reduced drinking, we will use empirically based guidelines for non-hazardous drinking (49). These call for men to consume no more than 3 standard drinks per day and 12 standard drinks per week and women to consume no more than 2 drinks per day and 8 drinks per week. Thus, patients will be counseled both to avoid heavy drinking days and to increase the number of abstinent days.

Patients will receive MM at each treatment visit. The first MM session will last 30 minutes and subsequent sessions 20 minutes. At each session, the nurse checks the patient's BAL, vital signs, weight, adverse effects, medication adherence, and concurrent medications; performs a brief assessment of the patient's drinking and general functioning; and makes recommendations for the patient to follow until the next visit. Patients with severe psychological symptoms (e.g., suicidal thoughts judged by a study physician to be clinically significant) will be withdrawn from treatment and referred for care.

D.4.b.1. Ensuring Adherence to MM Content and Procedures: Ms. Kaempf, the lead nurse practitioner, has more than 10 years of experience with MM, including in our completed TOP trial. She will train the nurses in the administration of MM by reviewing the protocol and manual with them, conducting role-playing and practice sessions, and reviewing audiotaped practice sessions until the nurses achieve adequate performance. Ms. Kaempf will also listen to 10% of recorded visits, evaluate the nurse practitioners' adherence to MM principles, record the total session time, assess the therapeutic relationship, and review the achievement of reduced drinking goals and clinical improvement during treatment. She will provide individual feedback to nurses (as needed) in monthly meetings to assure protocol adherence. Audiotapes will be destroyed after review. Her time will be contributed by the VISN 4 MIRECC.

D.5. Assessments: We include measures from different sources (see Table 2 below) to cover the various domains in which alcohol treatment may exert an effect and to corroborate treatment effects.

D.5.a. Laboratory/Medical Assessments: These assessments serve: 1) to screen patients for medical exclusion criteria, 2) to assess potential adverse effects of TOP, and 3) to corroborate self-reported drinking. Prior to entrance into the study, each patient will receive a physical examination, urinalysis and urine toxicology, complete blood count (CBC), a chemistry panel [which includes electrolytes, liver enzymes (ASAT, ALAT, %dCDT), bilirubin, uric acid, blood urea nitrogen (BUN), and creatinine], and pregnancy testing. Pregnancy testing will be repeated monthly. If at screening, a patient is found to be pregnant, she will be excluded from participation and referred for obstetric evaluation. If the patient is found to be pregnant at one of

the follow-up tests, she will immediately be withdrawn from treatment with medication, referred for obstetric evaluation, and advised to discontinue all drinking. At the midpoint and end of the 12-week treatment phase, %dCDT will be repeated to corroborate self-reported alcohol consumption.

D.5.b. Psychological/Behavioral Assessments: Although TOP is hypothesized to have its greatest influence on heavy drinking, other assessments are included to evaluate improvement in multiple domains.

D.5.b.1. Areas assessed only at intake:

a. Enrollment Logs and Patient Tracking: Procedures designed to maintain confidentially include both formal training sessions for all RAs in the importance of procedures to be followed, as well as formal mechanisms for limiting access to all information that can link data to individual patients. Data forms do not include identifying information. To facilitate tracking, the PI will maintain, under a limited password, a computer file with the identity of patients, their ID numbers and information about how they can be reached. However, this file will contain no clinical data. At the time of initial contact, the RA will assign each patient a unique ID number, which will serve to represent patients during data entry and file management procedures.

***b. Sociodemographic/general patient information*:** During screening, an assessment of medical history, personal and family history of alcoholism, marital status, educational and occupational information and substance abuse treatment history will be obtained using questionnaires and interviews described below.

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

***d. Psychiatric diagnosis*:** The Structured Clinical Interview for DSM-5 (SCID) will be used to classify patients according to the presence or absence of standard psychiatric disorders according to DSM-5 criteria.

***e. Family history of alcohol dependence*:** The Family History Assessment Module systematically queries the patient about the presence of an alcohol use disorder (AUD) in relatives. The patient will provide information concerning parents' and siblings' history of AUD criteria without their being identified. We will examine family history in relation to any of the candidate variants as part of validating these as pharmacogenetic moderators.

D.5.b.2. Areas assessed only at treatment endpoint:

a. Overall condition at the end of treatment (for early withdrawal from the study): The Early Termination Form, indicating the patient's level of functioning at termination, will be completed by the nurse for any patients that leave treatment prematurely. The form is used to identify the reasons for early termination (e.g., non-response, adverse effects) and other relevant circumstances. Patients unable to return for the endpoint will be mailed all questionnaires (with a stamped envelope for ease of return) and then interviewed by telephone. Patients will be compensated to complete the assessments. Using this and similar methods, we have been successful in obtaining 90% of data from subjects in alcohol treatment trials.

D.5.b.3. Areas assessed at intake and end of treatment:

a. Alcohol use patterns: The Timeline Follow-back (TLFB) (50) will be used to estimate past 90-day drinking at intake and at every treatment visit going back in time from the last assessment. The TLFB is reliable and valid when used by trained interviewers.

b. Alcohol-related problems: The Short Index of Problems (SIP), a 15-item instrument, was derived from the 50-item DrInC (32) and measures a single factor of alcohol-related problems (51). It proved to be sensitive as a measure of treatment outcome in our completed trial of TOP (7). As in that study, SIP scores will be used to describe the pretreatment alcohol-related problem severity of the sample and for concurrent validation of self-reported drinking during treatment and follow-up.

D.5.b.4. Areas assessed at each visit

a*. Medication usage:* The primary measure of medication adherence is recording of the pills dispensed and those taken by the patient from blister cards. The blister cards are prepared by the research pharmacist to be given as weekly packets. Blister cards have several advantages over pill counts, MEMS caps or riboflavin, including low cost, direct feedback to the patient regarding adherence, and ease of delivery (52). The use of riboflavin has been particularly questioned as a measure on adherence (53). Patients will be asked to return the unused portion of study medication at each visit. They will be compensated $5 for each visit at which they return the medication container.

b. Medication adverse effects: Patients will provide subjective reports of side effects at each study visit using the Systematic Assessment for Treatment Emergent Effects (SAFTEE) interview, a widely used measure that has been standardized for use in alcohol treatment trials (54).

c. Psychological symptoms: 1) The Patient Health Questionnaire (PHQ-9), a 9-item self-report measure of depressive symptoms with a total score of 0-27, will be completed at each visit (55). This is useful both to characterize the sample for comparison with other study samples and for monitoring patients' safety.

d. Measures of treatment received: We will keep records of medication taken and additional treatment received, including individual and group substance abuse and psychiatric treatment and self-help group participation.

Table 2: Schedule of Assessments

Instrument	Rater	Patient Time	Screen	Baseline	Weekly/ Monthly	Endpt & F/U's
Review of Criteria & Informed Consent	**CL**	**20 min**	**X**			
Medical History & Physical Exam	**CL**	**20**		**X**		
Laboratory Tests (blood for DNA only at screening; urine for urinalysis and urine toxicology only at screening)	**Lab**	**5**	**Chem. panel, CBC, U/A, %dCDT**		**Midpoint: bicarb, %dCDT; Monthly: preg. test**	**%dCDT**
Demographic Interview	**RC**	**10**	**X**			
Locator Information	**RC**	**2**	**X**			
Structured Clinical Interview for DSM-5	**RC**	**30**	**X**			**X[b]**
Family History Assessment Method	**RC**	**10**	**X**			
Timeline Follow-Back Interview	**RC**	**20**	**X**		**X[a]**	**X**
Short Index of Problems	**P**	**15**		**X**		**X**
Patient's Health Questionnaire-9	**P**	**3**		**X**	**X**	**X**
Medication Usage	**RC**	**3**			**X**	**X**
Systematic Assessment for Treatment Emergent Effects	**P, CL**	**5**		**X**	**X**	**X**
Measures of Treatment Received	**P, CL, RC**	**5**		**X**	**X**	**X**
Other Medical Management Procedures	**P, CL**	**10**			**X**	**X[c]**
Early Termination Form	**CL**	**10**				**X[d]**

CL = Clinician (Nurse Practitioner or Physician); RC = Research Coordinator; P = Patient ; F/U = follow-up visits at 3- and 6 months post-treatment

[a]Timeline Follow-back data will be collected at each visit to cover the period since the last visit.

[b]AUD diagnosis only at Endpoint and Follow-up visits

[c]Only at Endpoint

[d]Only for patients who do not complete the 12-week treatment

D.5.c. Design and Methodological Considerations

D.5.c.1. We chose a 12-week treatment period to ensure that patients receive adequate exposure to TOP at a dosage adequate to produce a treatment effect. We will focus the analysis on the last six weeks of treatment, by which time the TOP dosage will be 200 mg/day, a dosage at which clear separation from placebo has been seen in prior studies (5-8).

D.5.c.2. We chose the 200-mg/day dosage of TOP, which was shown by Miranda et al. (8) and by us (7) to be well tolerated and to reduce heavy drinking significantly. The 300-mg dosage, although efficacious, resulted in significantly greater dropout than placebo in a multi-center trial (6).

D.5.c.3. We chose to use the immediate-release formulation of TOP, administered twice daily, rather than Trokendi XR™ or Quedxy XR™, which are new, once-daily formulations of TOP. We chose the immediate-release formulation of TOP because it is generic and inexpensive, and its use to treat AUD in the VAHS is growing rapidly (9). If TOP is efficacious in this study, it would be of potential interest to compare the efficacy and tolerability of the immediate-release and the once-daily TOP formulations, which is beyond the scope of the present proposal.

D.5.c.4. We will enroll actively drinking individuals with a goal of reduced drinking or abstinence because studies using these goals showed robust effects of TOP in reducing heavy drinking. Although we will include patients with a DSM-5 diagnosis of AUD, we will require that patients have a weekly average of ≥2 heavy drinking days during the month before screening, consistent with the inclusion criteria for our TOP study in heavy drinkers (7). These criteria will enhance the study's external validity and applicability to the current diagnostic system while ensuring that we can detect a treatment effect on heavy drinking days.

D.5.c.5. We propose to use the MVP data to identify candidates for evaluation as moderators of the TOP response in AAs because it provides a large sample of Veterans whose demographics and other features would be most like the sample that we are recruiting for the proposed trial. Although Dr. Kranzler is one of the principal investigators on a beta project analyzing the GWAS data from the MVP for the phenotype of sustained heavy drinking, it may not be feasible to access the data for the purpose of the analyses proposed here. As a backup for that exploratory analysis, we will use data from our GWAS in AAs to which we have already have full access (11).

D.5.d. Rater reliability: We will aim to have the same rater interview each patient throughout the study, at the same time of day, to enhance the reliability of research ratings. We will conduct standardized rater training at the outset and ongoing quarterly assessments of performance to reduce "drift."

D.6. Genotyping: Data for this aim will come from a genomewide association study (GWAS) being conducted by the Million Veteran Program (MVP) or, alternatively, from GWAS data that we obtained in a sample of 3,318 AAs (11). We will collect a sample of whole blood to use for genotyping patients for the SNPs that are identified through beta testing of the MVP dataset as potential moderators of TOP response.

D.7. Data Analyses: The study will use the web-based direct entry data management system of the Penn Center for Studies of Addiction, with data stored on secure servers at the CMCVAMC. This arrangement has been approved and is described in a Memorandum of Understanding between the CMCVAMC and the Perelman School of Medicine at Penn. Interview data and self-report data are entered directly onto computers by research staff and/or subjects under supervision by staff. A range of checks for the validity of responses (including field validation to ensure that no out-of-range or otherwise invalid responses are accepted), and form validation (to ensure that logically impossible responses to different questions are not accepted) are built into this entry process. After entry, the research staff performs a brief review to ensure that the form has been completed. On completion of this review, the technician transmits the data (in 128-bit encrypted form) over the Internet to the DMU data servers. After a series of online reviews, the data are archived on the servers without protected health information. Audit logs record any modification to the original entry. Various levels of password protection will allow access to the data by members of the research team.

An important initial consideration will be to identify baseline differences between groups that may have occurred despite the use of block randomization. Prior to analysis, the distribution of outcome data will also be examined to determine the need for transformation and whether parametric analytic methods can be used.

D.7.a. To examine the effects of TOP treatment on the number of heavy drinking and abstinent days during the final six weeks of treatment (Specific Aim 1). The two primary outcomes, which will be measured using the TLFB, are the frequency of heavy drinking days (≥5 standard drinks in a day for men and ≥4 in a day for women), a sensitive, clinically relevant measure in alcohol treatment trials, and the frequency of abstinent days (56). An attempt will be made to evaluate outcomes for all patients irrespective of whether they continue to receive treatment, so that the analysis of all outcomes will be based on all of the data available for all randomized patients. Secondary outcomes for Aim 1 will include the severity of alcohol-related problems (i.e., SIP score) and %dCDT, which will be analyzed using models similar to those described below for the primary outcomes.

The two medication groups will be compared on weekly number of heavy drinking days and weekly number of abstinent days using mixed effects models for count responses, fitted using PROC GLIMMIX in SAS and the HGLM module of the HLM7 program (57). Estimates of effects over the final six weeks from the models, with associated standard errors and confidence intervals, will be used to test the primary hypotheses, i.e., that TOP treatment will reduce heavy drinking days and increase abstinent days more than placebo during the final six weeks of treatment. The models will include covariates for linear and quadratic time trends, as appropriate for model fit. The random effects will include a random intercept and, if necessary, residual autocorrelations, random slopes, or other specifications will be used. Although the primary contrasts will concentrate on the final six weeks, these models utilize all available data from all patients, so the analyses follow the intent-to-treat principle.

D.7.b. To explore the moderating effects of variation at *GRIK1* and other glutamate system genes on the efficacy of TOP 200 mg/day in reducing the frequency of heavy drinking and increasing the frequency of abstinent days (Specific Aim 2). Specific Aim 2 will be addressed by including a binary indicator of the SNPs identified as being associated to sustained heavy drinking through the MVP beta test project in the models described above for testing Specific Aims 1. These models will include the main effect of the SNP indicator and its interaction with medication group and time. Analyses will be conducted and results described as above. To identify candidate variants to test in the pharmacogenetic analyses, we will select SNPs in *GRIK1* and *GRIK2* (the genes that encode the GluK1 and GluK2 kainate subunits, on which TOP's effects are most potent and selective (39), using data from the MVP project, or alternatively from the GWAS that we completed on 3,318 AAs (11). We will select the 10 SNPs in these genes that yield the smallest p-values (ideally, but not necessarily, the p-values for these SNPs will be smaller than the p-value that is typically used to determine genomewide significance: $p<5.0X10^{-8}$). We will test for moderating effects by starting with the most significant SNP and continuing until one shows significance, with the value of α adjusted each time to reflect the number of comparisons (such that the tenth SNP would be tested using α=0.005). We will also construct a gene-based analysis, considering common variation mapped to genes that are implicated as being associated to sustained heavy drinking in the MVP sample or alcohol dependence in our sample (11). We will use the approach developed by Lin and et al. (58), where the interaction effect between an environment (treatment in our case) and all the SNPs within a gene can be considered in a unified framework. Analyses will be conducted and results described, as above. In particular, separate estimates and confidence intervals will be reported for the TOP effects in the two levels of each binary genotypic indicator. The outcomes for Aim 2 are exploratory.

D.7.c. To examine the persistence of effects of TOP treatment on the number of heavy drinking and abstinent days during a six-month post-treatment follow-up period (Specific Aim 3). We will use linear mixed models to examine medication group differences in percent heavy drinking days, percent days abstinent, SIP, GGTP, and %dCDT across the treatment and post-treatment periods. The 12-week treatment period, along with the 3-month and 6-month follow-up periods will be included in the analysis to determine whether the change in outcomes from treatment to follow-up differ by medication group. The models will include study period (treatment period, 3-month follow-up, 6-month follow-up), treatment group (TOP, placebo) and the interaction between these two factors to test for differences between study periods, treatment groups, and the change in the difference between groups across study periods. Baseline (pretreatment) values for each outcome will be included as covariates in modeling the respective outcome. The outcomes for Aim 3 are considered exploratory. We will also explore the persistence of TOP effects using the primary SNP identified in Aim 2. That is, we will conduct a pharmacogenetic analysis of the persistent effects of TOP, similar to our analysis of heavy drinking in EAs, where rs2832407*C homozygotes treated with TOP had robust reductions in heavy drinking during the six-month post-treatment period (10).

D.7.d. Dropout and Missing Data: We will base the primary relative efficacy comparisons in the trial on mixed effects models utilizing all data provided by participants. In our completed TOP trial, we saw limited dropout (8% to the start of the final six weeks, and 4% thereafter). We will assess the sensitivity of our assumption that missing data are ignorable by running models that address missingness in different ways. For mixed effects models, pattern mixture models test for differences in regression estimates across patterns of missing data, and shared parameter models allow for correlated random effects for the primary responses and the week-to-week binary indicators of missing/complete data (57). Semi-parametric regression models use inverse probability weighting to extend the validity of GEE models, and provide a different type of sensitivity analysis for the mixed effects models (59). All of these modeling approaches require certain model assumptions, so we will compare the results of the analyses over a range of such assumptions.

D.7.e. Adherence: To assess the sensitivity of the results of the analyses described above to non-adherence, the models described above for our primary and secondary outcomes will be extended using instrumental variable approaches. Under some assumptions, these analyses will yield estimates of the intervention effects that would have been seen in a study with full adherence. To analyze data using a single overall measure of adherence (e.g., 80% of assigned medication taken over the 12 weeks of treatment), we will use the methods of Nagelkerke et al. (60). We will also examine longitudinal extensions of these methods, looking at weekly adherence to medications as a time varying measure (61).

D.7.f. Adequacy of Sample Size for Specific Aim 1: The analyses described above make use of all data provided by all patients to estimate models from which contrasts restricted to the final six weeks will test the TOP effect on days of heavy drinking and abstinent days (**Specific Aim 1**). Power for the contrasts will be determined by the patterns of outcomes in the final six weeks, so power estimates are based on weeks 7

through 12 as a 6-week trial, with adjustments for loss to attrition between baseline and week 6. Based on our prior study (7) we anticipate 92% retention through the first six weeks for each group, yielding 74 available per group at the end of week 6, an additional 4% loss due to dropout across the final six weeks, and a within-subject correlation of about 0.6. The methods of Hedeker et al show that we will have 80% power for a TOP main effect size of d=0.40, 0.43, and 0.46, for within-subject correlations of 0.5, 0.6, and 0.7, respectively, at a corrected alpha level of 0.025 (62). In Kranzler et al, the effect sizes for heavy drinking days in weeks 7 through 12 varied between d=0.52 and d=0.62, so the sample size should be adequate to detect similar effects in the current study (7).

D.7.g. Adequacy of Sample Size for Specific Aims 2 and 3: The analyses to address these aims are based on the expectation that genetic variation will be identified that moderates the response to TOP in AAs, in a manner analogous to that seen in EAs, in which the most robust post-treatment effects were observed in individuals with a specific TOP-responsive genotype (10). We acknowledge that the sample may not be large enough to provide adequate power for definitive analyses for these Aims. However, we believe that the knowledge gained, including estimates of effect sizes of moderator effects (**Specific Aim 2**) and persistent effects (**Specific Aim 3**), will inform subsequent TOP studies in AAs with AUD.

D.7.h. Safety: Safety will be analyzed using categorical outcomes, defined by the type and severity of adverse effects. Summary measures of adverse events will be developed by organ system from the SAFETEE and will be compared for patients receiving TOP or placebo using chi-square analysis.

Table 3: Timeline of Performance Goals

Activity	Year 1				Year 2				Year 3				Year 4				Year 5			
Staff training and study initiation	■																			
Patient enrollment		■	■	■	■	■	■	■	■	■	■	■	■	■	■					
Endpoint assessments			■	■	■	■	■	■	■	■	■	■	■	■	■	■				
Follow-up Assessments				■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Data cleaning				■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Data analysis																	■	■	■	■
Report writing																		■	■	■

REFERENCES

1. Caetano R. Alcohol-related health disparities and treatment-related epidemiological findings among whites, blacks, and Hispanics in the United States. Alcoholism, clinical and experimental research. 2003;27(8):1337-9. doi: 10.1097/01.ALC.0000080342.05229.86. PubMed PMID: 12966334.
2. Stinson FS, Grant BF, Dufour MC. The critical dimension of ethnicity in liver cirrhosis mortality statistics. Alcoholism, clinical and experimental research. 2001;25(8):1181-7. PubMed PMID: 11505049.
3. Ray LA, Oslin DW. Naltrexone for the treatment of alcohol dependence among African Americans: results from the COMBINE Study. Drug and alcohol dependence. 2009;105(3):256-8. doi: 10.1016/j.drugalcdep.2009.07.006. PubMed PMID: 19717248; PubMed Central PMCID: PMC3409877.
4. Blodgett JC, Del Re AC, Maisel NC, Finney JW. A meta-analysis of topiramate's effects for individuals with alcohol use disorders. Alcoholism, clinical and experimental research. 2014;38(6):1481-8. doi: 10.1111/acer.12411. PubMed PMID: 24796492; PubMed Central PMCID: PMC4047180.
5. Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, Javors MA, Ma JZ. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial.[comment]. Lancet. 2003;361(9370):1677-85.
6. Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K, McKay A, Ait-Daoud N, Anton RF, Ciraulo DA, Kranzler HR, Mann K, O'Malley SS, Swift RM. Topiramate for treating alcohol dependence: a randomized controlled trial. Journal of the American Medical Association. 2007;298(14):1641-51. Epub 2007/10/11. doi: 10.1001/jama.298.14.1641. PubMed PMID: 17925516.
7. Kranzler HR, Covault J, Feinn R, Armeli S, Tennen H, Arias AJ, Gelernter J, Pond T, Oncken C, Kampman KM. Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. The American journal of psychiatry. 2014;171(4):445-52. doi: 10.1176/appi.ajp.2013.13081014. PubMed PMID: 24525690; PubMed Central PMCID: PMC3997125.
8. Miranda R, Jr., MacKillop J, Monti PM, Rohsenow DJ, Tidey J, Gwaltney C, Swift R, Ray L, McGeary J. Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. Alcoholism, clinical and experimental research. 2008;32(3):489-97. Epub 2008/01/25. doi: 10.1111/j.1530-0277.2007.00592.x. PubMed PMID: 18215213.
9. Del Re AC, Gordon AJ, Lembke A, Harris AH. Prescription of topiramate to treat alcohol use disorders in the Veterans Health Administration. Addiction science & clinical practice. 2013;8:12. doi: 10.1186/1940-0640-8-12. PubMed PMID: 23835352; PubMed Central PMCID: PMC3716908.
10. Kranzler HR, Wetherill R, Feinn R, Pond T, Gelernter J, Covault J. Posttreatment effects of topiramate treatment for heavy drinking. Alcoholism, clinical and experimental research. 2014;38(12):3017-23. doi: 10.1111/acer.12578. PubMed PMID: 25581656; PubMed Central PMCID: PMC4293099.
11. Gelernter J, Kranzler HR, Sherva R, Almasy L, Koesterer R, Smith AH, Anton R, Preuss UW, Ridinger M, Rujescu D, Wodarz N, Zill P, Zhao H, Farrer LA. Genome-wide association study of alcohol dependence:significant findings in African- and European-Americans including novel risk loci. Molecular psychiatry. 2014;19(1):41-9. doi: 10.1038/mp.2013.145. PubMed PMID: 24166409; PubMed Central PMCID: PMC4165335.
12. Office of Applied Studies. Results from the 2005 National Survey on Drug Use and Health: National Findings Substance Abuse and Mental Health Services Administration. Rockville MD: 2006 DHHS Publication No. SMA 06-4194.
13. Center for Behavioral Health Statistics and Quality. 2014 National Survey on Drug Use and Health: Detailed Tables. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2015.
14. Williams EC, Gupta S, Rubinsky AD, Jones-Webb R, Bensley KM, Young JP, Hagedorn H, Gifford E, Harris AH. Racial/Ethnic Differences in the Prevalence of Clinically Recognized Alcohol Use Disorders Among Patients from the U.S. Veterans Health Administration. Alcoholism, clinical and experimental research. 2016;40(2):359-66. doi: 10.1111/acer.12950. PubMed PMID: 26842254.
15. Bush K, Kivlahan D, McDonell M, Fihn S, Bradley K. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Archives of internal medicine. 1998;158:1789-95.

16. Glass JE, Perron BE, Ilgen MA, Chermack ST, Ratliff S, Zivin K. Prevalence and correlates of specialty substance use disorder treatment for Department of Veterans Affairs Healthcare System patients with high alcohol consumption. Drug and alcohol dependence. 2010;112(1-2):150-5. Epub 2010/07/27. doi: 10.1016/j.drugalcdep.2010.06.003. PubMed PMID: 20656425; PubMed Central PMCID: PMC2967645.
17. Kirchner JE, Booth BM, Owen RR, Lancaster AE, Smith GR. Predictors of patient entry into alcohol treatment after initial diagnosis. The journal of behavioral health services & research. 2000;27(3):339-46. PubMed PMID: 10932447.
18. Williams EC, Lapham GT, Hawkins EJ, Rubinsky AD, Morales LS, Young BA, Bradley KA. Variation in documented care for unhealthy alcohol consumption across race/ethnicity in the Department of Veterans Affairs Healthcare System. Alcoholism, clinical and experimental research. 2012;36(9):1614-22. doi: 10.1111/j.1530-0277.2012.01761.x. PubMed PMID: 22404130.
19. Chartier KG, Caetano R. Trends in alcohol services utilization from 1991-1992 to 2001-2002: ethnic group differences in the U.S. population. Alcoholism, clinical and experimental research. 2011;35(8):1485-97. doi: 10.1111/j.1530-0277.2011.01485.x. PubMed PMID: 21575015; PubMed Central PMCID: PMC3143282.
20. Rosner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. The Cochrane database of systematic reviews. 2010(12):CD001867. doi: 10.1002/14651858.CD001867.pub2. PubMed PMID: 21154349.
21. Rosner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. The Cochrane database of systematic reviews. 2010(9):CD004332. doi: 10.1002/14651858.CD004332.pub2. PubMed PMID: 20824837.
22. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA : the journal of the American Medical Association. 2014;311(18):1889-900. Epub 2014/05/16. doi: 10.1001/jama.2014.3628. PubMed PMID: 24825644.
23. Garbutt J, Kranzler H, O'Malley S, Gastfriend D, Pettinnat iH, Silverman B. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. J Am Med Assoc. 2005;293:1617-25.
24. Harris AH, Oliva E, Bowe T, Humphreys KN, Kivlahan DR, Trafton JA. Pharmacotherapy of alcohol use disorders by the Veterans Health Administration: patterns of receipt and persistence. Psychiatr Serv. 2012;63(7):679-85. Epub 2012/05/03. doi: 10.1176/appi.ps.201000553. PubMed PMID: 22549276.
25. Petrakis IL, Leslie D, Rosenheck R. Use of naltrexone in the treatment of alcoholism nationally in the Department of Veterans Affairs. Alcoholism, clinical and experimental research. 2003;27(11):1780-4. doi: 10.1097/01.ALC.0000095861.43232.19. PubMed PMID: 14634494.
26. Givens JL, Houston TK, Van Voorhees BW, Ford DE, Cooper LA. Ethnicity and preferences for depression treatment. General hospital psychiatry. 2007;29(3):182-91. doi: 10.1016/j.genhosppsych.2006.11.002. PubMed PMID: 17484934.
27. Jimenez DE, Bartels SJ, Cardenas V, Dhaliwal SS, Alegria M. Cultural beliefs and mental health treatment preferences of ethnically diverse older adult consumers in primary care. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2012;20(6):533-42. doi: 10.1097/JGP.0b013e318227f876. PubMed PMID: 21992942; PubMed Central PMCID: PMC3258470.
28. Plebani JG, Oslin DW, Lynch KG. Examining naltrexone and alcohol effects in a minority population: results from an initial human laboratory study. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2011;20(4):330-6. doi: 10.1111/j.1521-0391.2011.00138.x. PubMed PMID: 21679264; PubMed Central PMCID: PMC3124087.
29. Rubio G, Ponce G, Jimenez-Arriero MA, Palomo T, Manzanares J, Ferre F. Effects of topiramate in the treatment of alcohol dependence. Pharmacopsychiatry. 2004;37(1):37-40. doi: 10.1055/s-2004-815473. PubMed PMID: 14750047.
30. Paparrigopoulos T, Tzavellas E, Karaiskos D, Kourlaba G, Liappas I. Treatment of alcohol dependence with low-dose topiramate: an open-label controlled study. BMC psychiatry. 2011;11:41. doi: 10.1186/1471-244X-11-41. PubMed PMID: 21401921; PubMed Central PMCID: PMC3062593.
31. Likhitsathian S, Uttawichai K, Booncharoen H, Wittayanookulluk A, Angkurawaranon C, Srisurapanont M. Topiramate treatment for alcoholic outpatients recently receiving residential treatment programs: a 12-week,

randomized, placebo-controlled trial. Drug and alcohol dependence. 2013;133(2):440-6. doi: 10.1016/j.drugalcdep.2013.06.032. PubMed PMID: 23906999.
32. Miller W, Tonigan J, Longabaugh R. The Drinker Inventory of Consequences (DrInC): An instrument for assessing adverse consequences of alcohol abuse. Washington, D.C: U.S. Government Printing Office; 1995.
33. Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, Kerse N, Macgillivray S. Antidepressants versus placebo for depression in primary care. The Cochrane database of systematic reviews. 2009(3):CD007954. doi: 10.1002/14651858.CD007954. PubMed PMID: 19588448.
34. Feinn R, Curtis B, Kranzler H. Balancing Risk and Benefit in Heavy Drinkers Treated With Topiramate: Implications for Personalized Care. Journal of Clinical Psychiatry. (in press);77.
35. White HS, Brown SD, Woodhead JH, Skeen GA, Wolf HH. Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. Epilepsia. 2000;41 Suppl 1:S17-20. PubMed PMID: 10768294.
36. Skradski S, White HS. Topiramate blocks kainate-evoked cobalt influx into cultured neurons. Epilepsia. 2000;41 Suppl 1:S45-7. PubMed PMID: 10768300.
37. Gibbs JW, 3rd, Sombati S, DeLorenzo RJ, Coulter DA. Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. Epilepsia. 2000;41 Suppl 1:S10-6. PubMed PMID: 10768293.
38. McDonald R, Rogawski M. Cellular effects of antiepileptic drugs. In: Engel J, Pedley E, editors. Epilepsy: A Comprehensive Textbook, Second Edition. Philadelphia, PA: Williams and Wilkins; 2006. p. 1433-46.
39. Gryder DS, Rogawski MA. Selective antagonism of GluR5 kainate-receptor-mediated synaptic currents by topiramate in rat basolateral amygdala neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2003;23(18):7069-74. PubMed PMID: 12904467.
40. Kranzler HR, Gelernter J, Anton RF, Arias AJ, Herman A, Zhao H, Burian L, Covault J. Association of markers in the 3' region of the GluR5 kainate receptor subunit gene to alcohol dependence. Alcoholism, clinical and experimental research. 2009;33(5):925-30. Epub 2009/03/27. doi: 10.1111/j.1530-0277.2009.00913.x. PubMed PMID: 19320626; PubMed Central PMCID: PMC2772659.
41. Ray LA, Miranda R, Jr., MacKillop J, McGeary J, Tidey JW, Rohsenow DJ, Gwaltney C, Swift RW, Monti PM. A preliminary pharmacogenetic investigation of adverse events from topiramate in heavy drinkers. Experimental and clinical psychopharmacology. 2009;17(2):122-9. doi: 10.1037/a0015700. PubMed PMID: 19331489; PubMed Central PMCID: PMC3682424.
42. Oslin DW, Berrettini W, Kranzler HR, Pettinati H, Gelernter J, Volpicelli JR, O'Brien CP. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2003;28(8):1546-52. doi: 10.1038/sj.npp.1300219. PubMed PMID: 12813472.
43. Kranzler HR, Armeli S, Covault J, Tennen H. Variation in OPRM1 moderates the effect of desire to drink on subsequent drinking and its attenuation by naltrexone treatment. Addiction biology. 2013;18(1):193-201. Epub 2012/07/13. doi: 10.1111/j.1369-1600.2012.00471.x. PubMed PMID: 22784013; PubMed Central PMCID: PMC3473112.
44. Crist RC, Berrettini WH. Pharmacogenetics of OPRM1. Pharmacology, biochemistry, and behavior. 2013. Epub 2013/11/10. doi: 10.1016/j.pbb.2013.10.018. PubMed PMID: 24201053.
45. Pettinati H, Weiss R, Miller W, Donovan D, Ernst D, BJ R. Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence. Bethesda, MD: NIAAA, DHHS Publication # 04-5289; 2004.
46. Tang H, Quertermous T, Rodriguez B, Kardia SL, Zhu X, Brown A, Pankow JS, Province MA, Hunt SC, Boerwinkle E, Schork NJ, Risch NJ. Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. American journal of human genetics. 2005;76(2):268-75. doi: 10.1086/427888. PubMed PMID: 15625622; PubMed Central PMCID: PMC1196372.
47. Kaufman H. The Slosson intelligence test as a screening instrument with a rehabilitation population. Exceptional children. 1969;35(9):745. PubMed PMID: 5786372.
48. Pittman B, Gueorguieva R, Krupitsky E, Rudenko AA, Flannery BA, Krystal JH, Pittman B, Gueorguieva R, Krupitsky E, Rudenko AA, Flannery BA, Krystal JH. Multidimensionality of the Alcohol Withdrawal

Symptom Checklist: a factor analysis of the Alcohol Withdrawal Symptom Checklist and CIWA-Ar. Alcoholism: Clinical & Experimental Research. 2007;31(4):612-8. PubMed PMID: 17374040.
49. Sanchez-Craig M. Drinking alcohol: a guide for evaluating and changing drinking patterns. Toronto1995.
50. Sobell LC, Brown J, Leo GI, Sobell MB. The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. Drug and alcohol dependence. 1996;42(1):49-54. PubMed PMID: 8889403.
51. Feinn R, Tennen H, Kranzler HR, Feinn R, Tennen H, Kranzler HR. Psychometric properties of the short index of problems as a measure of recent alcohol-related problems. Alcoholism: Clinical & Experimental Research. 2003;27(9):1436-41. PubMed PMID: 14506404.
52. Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify nonadherence. The Annals of pharmacotherapy. 2009;43(3):413-22. doi: 10.1345/aph.1L496. PubMed PMID: 19261962.
53. Anton R. New methodologies for pharmacological treatment trials for alcohol dependence. Alcoholism: Clinical and Experimental Research. 1996;20:3A - 9A.
54. Johnson BA, Ait-Daoud N, Roache JD. The COMBINE SAFTEE: a structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field. Journal of studies on alcohol Supplement. 2005(15):157-67; discussion 40. Epub 2005/10/15. PubMed PMID: 16223067.
55. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of General Internal Medicine. 2001;16(9):606-13.
56. Falk D, Wang XQ, Liu L, Fertig J, Mattson M, Ryan M, Johnson B, Stout R, Litten RZ. Percentage of subjects with no heavy drinking days: evaluation as an efficacy endpoint for alcohol clinical trials. Alcoholism, clinical and experimental research. 2010;34(12):2022-34. doi: 10.1111/j.1530-0277.2010.01290.x. PubMed PMID: 20659066.
57. Molenberghs G, Verbeke G. Models for Discrete Longitudinal Data: Springer; 2006.
58. Lin X, Lee S, Christiani DC, Lin X. Test for interactions between a genetic marker set and environment in generalized linear models. Biostatistics. 2013;14(4):667-81. doi: 10.1093/biostatistics/kxt006. PubMed PMID: 23462021; PubMed Central PMCID: PMC3769996.
59. Rotnitzky A, Robins J, Scharfstein D. Semiparametric regression models for repeated outcomes with nonignorable nonresponse. Journal of the American Statistical Association. 1998;93:1321 - 39.
60. Nagelkerke N, Fidler V, Bernsen R, Borgdorff M. Estimating treatment effects in randomized clinical trials in the presence of non-compliance. Statistics in medicine. 2000;19:1849 - 64.
61. Small DS, Ten Have TR, Joffe MM, Cheng J. Random effects logistic models for analysing efficacy of a longitudinal randomized treatment with non-adherence. Statistics in medicine. 2006;25(12):1981-2007. Epub 2005/10/13. doi: 10.1002/sim.2313. PubMed PMID: 16220487.
62. Hedeker D, Mermelstein RJ, Weeks KA. The thresholds of change model: an approach to analyzing stages of change data. Ann Behav Med. 1999;21(1):61-70. Epub 2008/04/22. doi: 10.1007/BF02895035. PubMed PMID: 18425656.