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Topiramate Treatment of Heavy Drinkers: Moderation by a *GRIK1* Polymorphism

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Abstract

Objective: Topiramate has been shown to reduce drinking and heavy drinking in alcohol-dependent individuals whose goal was to *stop* drinking. The present study evaluated the efficacy and tolerability of topiramate in heavy drinkers whose treatment goal was to *reduce* drinking to safe levels.

Method: We randomly assigned 138 individuals (62.3% male) to receive 12 weeks of treatment with topiramate (N=67), at a maximal daily dosage of 200 mg, or matching placebo (N=71), both groups receiving brief counseling to reduce drinking and increase abstinent days. We hypothesized that topiramate-treated patients would be better able to achieve these goals and predicted that, based on prior research, the effects would be moderated by a single nucleotide polymorphism (rs2832407) in *GRIK1*, encoding the kainate GluK1 receptor subunit.

Results: The rate of treatment completion was 84.9% and equal by treatment group. Topiramate treatment significantly reduced heavy drinking days ($p<0.001$) and increased abstinent days

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(p=0.032) relative to placebo. The topiramate group also had lower concentrations of the liver enzyme γ-glutamyltranspeptidase and lower scores on a measure of alcohol-related problems than the placebo group. In a European-American subsample (N=122), topiramate's effect on heavy drinking days (p=0.004) was significantly greater than for placebo only in rs2832407 C-allele homozygotes.

Conclusions: These findings support the use of topiramate 200 mg/day to reduce heavy drinking in problem drinkers. The moderator effect of rs2832407, if validated, would facilitate the identification of heavy drinkers who are likely to respond well to topiramate treatment and provide an important personalized treatment option. The pharmacogenetic findings also implicate the kainate receptor in the mechanism of topiramate's effects on heavy drinking.
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Introduction

Heavy drinking is common in the United States. In 2010, 23.1% of U.S. individuals age 12 or older reported that, during the prior month, they drank five or more drinks on an occasion and 6.7% reported doing so on at least five days. As the frequency of heavy drinking increases, so does the incidence of a variety of alcohol-related problems, including alcohol use disorder (2). Despite these risks, only a small fraction of heavy drinkers in the population receive any kind of alcohol treatment, with medications particularly underutilized (3).

Further, the development of alcohol treatment medications has focused on patients who meet criteria for alcohol dependence, particularly patients whose treatment goal is abstinence, rather than reduced drinking. Some studies of opioid antagonists are exceptions to this (4-8).

Although topiramate has shown substantial promise in reducing drinking in patients whose ultimate goal was abstinence (9,10), there are no studies of its efficacy in treating heavy drinkers who aim to reduce their drinking. In an initial single-site 12-week study of topiramate (9), alcohol-dependent patients that received 300 mg/day of the drug (N=75) had a lower percentage of heavy drinking days than placebo-treated patients (N=75). This effect was replicated in a 14-week multicenter trial of 371 patients (10). In a study in non-treatment-seeking subjects, Miranda et al. (11) randomly assigned 61 individuals to receive 39 days of treatment with topiramate 200 mg/day, topiramate 300 mg/day, or placebo. They found that the frequency of heavy drinking was significantly lower in both topiramate groups than with placebo.

Topiramate has multiple pharmacologic effects, including the facilitation of GABAergic function by interacting with a non-benzodiazepine site on the $GABA_A$ receptor (12) and antagonism of glutamate activity at AMPA and kainate receptors (13-14). Topiramate's effects on glutamate receptors are most potent and selective for those containing the GluK1 (formerly called GluR1) subunit (encoded by *GRIK1)* (16-17). Topiramate also blocks voltage-dependent Na^+ and L-type voltage-gated Ca^{++} channels, inhibits carbonic anhydrase, and enhances K^+ conductance (15).

To identify potential moderators of topiramate response, Kranzler et al. (18) examined the association of seven single nucleotide polymorphisms (SNPs) in *GRIK1* to the risk of alcohol dependence. One SNP, rs2832407, a C-to-A non-coding substitution, was significantly associated with alcohol dependence, with the C-allele being more common in alcohol-dependent subjects. Ray et al. (19) showed that, when treated with topiramate, *GRIK1**rs2832407 C-allele homozygotes experienced significantly fewer adverse medication effects than A-allele carriers.

The present study tested two hypotheses: first, that the group receiving topiramate would show a greater reduction in the number of heavy drinking days and a greater increase in the number of abstinent days than the placebo group and second, that *GRIK1**rs2832407 would moderate the response to topiramate. Support for these hypotheses would provide an important option for the personalized treatment of heavy drinking.

Method

Overview

The study was a parallel-groups, placebo-controlled trial of topiramate in heavy drinkers, all of whom received medical management (20), a brief psychosocial intervention, at each of 9 treatment visits. Patients were randomly assigned to treatment group and double-blind conditions were maintained throughout the study. Raters were trained in the reliable use of all assessments. The study was conducted in three phases: a one-week pre-treatment assessment period, a 12-week treatment period, and a 9-day medication taper period.

Patients

Inclusion criteria were age 18-65 years; an average weekly consumption of ≥24 standard drinks for men and ≥18 standard drinks for women; an explicit goal of reducing drinking to safe levels; ability to read English at a level of ≥8th grade; no gross evidence of cognitive impairment; willingness to name a potential locator to ensure follow up; and written, informed consent to participate. Women of childbearing potential had to be non-lactating and practicing a reliable method of birth control, and to have a negative serum pregnancy test at screening.

Exclusion criteria were the presence of a current, clinically significant physical disease or abnormality on the basis of medical history, physical examination, or routine laboratory evaluation; history of nephrolithiasis; serious psychiatric illness by history or examination; a current DSM-IV diagnosis of drug (other than nicotine) dependence; and evidence of likely need for abstinence from alcohol (i.e., current severe alcohol dependence, disorders exacerbated by heavy drinking (e.g., gastritis), self-reported inability to reduce drinking, or current alcohol withdrawal symptoms or a history of past severe withdrawal symptoms.

We screened 200 prospective participants in person, of whom 138 patients (86 men, 62.3%) were randomly assigned to treatment with topiramate (N=67, 48.6%) or placebo (N=71, 51.4%). Supplemental Figure S1 is a CONSORT diagram. The study was initiated at the University of Connecticut Health Center (N=76) and completed at the University of

Pennsylvania Treatment Research Center (N=62); both institutional review boards approved the study protocol. Patients were paid to complete research assessments.

Procedures

Subjects were recruited through advertisements. An initial telephone screening interview was followed by an in-person visit, where patients gave written, informed consent to participate and underwent a history, physical examination, routine laboratory testing, a urine drug screen, and pregnancy testing (as appropriate).

Prior to randomization, patients completed questionnaires and were administered research interviews by a trained research evaluator. A nurse then administered the first medical management session and dispensed study medication. We balanced the medication groups on age, sex, and the frequency of drinking days and heavy drinking days during pretreatment using urn randomization and stratified the randomization for patients taking antidepressants.

During the first six weeks of treatment, patients were seen weekly for medication titration, followed by three biweekly visits. At each visit, the patient's breath alcohol concentration, weight, and vital signs were measured; patients completed questionnaires; and the research nurse elicited information on concurrent medications, the occurrence of adverse events, and protocol adherence, and delivered the medical management intervention (20). At each visit, patients were interviewed to measure drinking and medication usage since the last visit. The nurse compared self-reported adherence to the number of capsules returned and discussed discrepancies with the patient to resolve them. At the end of treatment, patients again completed questionnaires and were interviewed by the research nurse and the research evaluator.

Study Treatments

Counseling—The medical management manual focuses on medication adherence and treatment participation through education and support; it was modified to be consistent with a goal of sensible drinking. The initial session included a review of the results of the initial evaluation and a discussion of sensible drinking limits using *A Guide to Sensible Drinking* (21), and a rationale for and information about pharmacotherapy and the importance of medication adherence. At subsequent sessions (20-30 minutes), the nurse briefly assessed the patient’s drinking, monitored medication adherence, and made recommendations related to both. Based on guidelines for non-hazardous drinking (22), men were advised to consume no more than 3 standard drinks per day and 12 standard drinks per week and women were advised to consume no more than 2 drinks per day and 8 drinks per week. Thus, patients were counseled both to avoid heavy drinking days and to increase the number of abstinent days. Sessions were audiotaped and reviewed and feedback provided to nurses to ensure consistency in their delivery.

Medication—We selected a maximal dosage of 200 mg/day of topiramate based on evidence of its efficacy (9-11) and to limit the adverse effects associated with a higher medication dosage (10). Topiramate treatment was initiated at a dosage of 25 mg at bedtime and at weekly intervals was increased as follows: 50 mg at bedtime, then 25 mg in the

morning and 50 mg at bedtime, then 50 mg twice daily, then 50 mg in the morning and 100 mg at bedtime, and, finally, 100 mg twice daily. Placebo and topiramate were encapsulated and indistinguishable from one another. Dosage reductions or a delay in the increase were used to manage adverse effects.

Assessments

Laboratory Assessments included urinalysis and urine toxicology testing, a complete blood count, γ-glutamyltranspeptidase concentration, and a chemistry panel (including electrolytes, liver enzymes, and bilirubin). Electrolytes were repeated at the study midpoint to screen for metabolic acidosis. Measurement of γ-glutamyltranspeptidase was repeated at the midpoint and end treatment to validate self-reported drinking.

Psychological/Behavioral Assessments.

a. Sociodemographic/clinical information included marital status, educational and occupational information, medical history, and substance abuse treatment history.

b. Psychiatric diagnosis: The Structured Clinical Interview for DSM-IV (23) was used to classify patients according to the presence or absence of standard psychiatric disorders according to DSM-IV (24).

c. Alcohol use patterns: The Timeline Follow-back Method (25) was used to estimate the number of abstinent days and heavy drinking days during the 90-day pretreatment period and at each treatment visit.

d. Alcohol-related problems: The Short Index of Problems (26), a 15-item, single-factor measure of alcohol-related problems (27), was administered at baseline and study endpoint.

e. Depressive symptoms: The Beck Depression Inventory (28), a 21-item self-report measure of depressive symptoms (score=0-63; 27), was administered at baseline. It was repeated at every study visit for patients receiving an antidepressant or whose depression score was elevated at baseline.

Statistical Analysis

Descriptive statistics include means and standard deviations for continuous variables (group differences analyzed using t-tests) and percentages for categorical variables (group differences analyzed using chi-square). Factorial models crossing treatment assignment with 3-level genotype group were analyzed using the general linear model for continuous variables and logistic regression for dichotomous categorical variables.

Timeline Follow-back Data—Drinking data were aggregated to the weekly level. The number of days/week of heavy drinking (i.e., ≥4 drinks in a day for women and ≥5 drinks in a day for men) and of abstinence were the primary outcomes. Generalized linear mixed models with a binomial distribution and logit link function were used to examine medication group differences in changes in these outcomes during treatment. The models included fixed effects for medication group, week, and the interaction between medication and week, and a random effect for intercept. “Week” was recoded by subtracting the number of weeks of the

study (12) so that the test of treatment compared groups at the conclusion of the study, week 12, rather than at baseline. The interaction term tested for different rates of change in the outcome during the study.

Two sets of analyses of the number of heavy drinking and abstinent days were conducted. First, an intent-to-treat analysis included all 138 patients. In addition to examining changes in drinking over time, we conducted a responder analysis that examined the number of patients in each group with no heavy drinking days during the last four weeks of treatment, consistent with the approach recommended by the Food and Drug Administration (29). Second, we conducted a pharmacogenetic analysis that was limited to self-identified European-American patients (N=122) due to substantial population differences in rs2832407 allele frequency. Initially, we used the three-level genotype for rs2832407 by adding it to the linear mixed analysis. We then combined the AA and AC groups, comparing them with the CC group as a dichotomous genotype.

Timeline follow-back data were available for 92.4% (SD=22.7) of the 84 days of treatment [92.9% (SD=20.9) in topiramate patients and 91.9% (SD=24.5) in placebo patients]. To examine the impact of missing data, multiple imputation using Markov Chain Monte Carlo single chain, based on patient baseline characteristics and weekly drinking, was employed to create 10 imputed data sets. Models were re-run on the imputed data sets using SAS *proc mianalyze*.

Measures to Validate Drinking Outcomes—γ-glutamyltranspeptidase concentrations were analyzed at the study midpoint and endpoint. Due to severe positive skewness and kurtosis the values were log transformed. The Short Index of Problems score was analyzed using ANCOVA, controlling for the pretreatment score.

Results

DSM-IV Diagnoses and Antidepressant Treatment

Although a DSM-IV diagnosis of current alcohol dependence was not an inclusion criterion, the vast majority of patients (92.5% of topiramate patients and 91.5% of placebo patients) met criteria for the diagnosis. Despite a high lifetime prevalence of major depression (see Table 1), only three patients in the topiramate group and five patients in the placebo group met current criteria for an anxiety or depressive disorder. A total of 23 patients were taking antidepressants at the time of randomization (16.4% of topiramate patients and 16.9% of placebo patients).

Treatment Completion

Treatment completers were those who completed 12 weeks of treatment. Overall, 117 subjects (84.9%) completed treatment [topiramate: n=55, 82.1%; placebo: n=62, 87.3%; $\chi^2_{(1)}$=0.73, p=0.39]. The medication groups were comparable on the number of weeks of treatment received [topiramate: mean=10.9, SD=2.6, placebo: mean=11.1, SD=2.7; $F_{(1,136)}$=0.14), p=0.70). In European Americans, there was no main effect of genotype group [$F_{(2,116)}$=1.62, p=0.20] or interaction of genotype group with medication group [$F_{(2,116)}$=0.38, p=0.69] on treatment weeks.

Medication Adherence and Maximal Dosage Achieved

Using self-reports, with verification by capsule counts, there was a high rate of adherence in both medication groups [placebo: mean=91.1% of doses (SD=24.7); topiramate: 89.4% of doses (SD=23.1); $F_{(1,135)}$= 0.11, p=0.67]. Nonetheless, there was a non-significant trend [$F_{(1,136)}$=3.53, p=0.063] for placebo patients to take a higher dosage of the study medication [equivalent dosage=187.7 mg (SD=43.1)] than topiramate patients [173.5 mg (SD=45.6)]. In European Americans, there was no difference in maximal dosage by genotype group [$F_{(2,116)}$=0.55 , p=0.58] or the interaction of genotype group with medication group [$F_{(2,116)}$=0.04, p=0.96].

Main Effects of Topiramate

Demographic and pretreatment clinical measures: The study sample consisted predominantly of middle-aged, European-American, married, employed men, with an average of three years of college (Table 1). During pretreatment, patients drank alcohol approximately 6 days/week and drank heavily 5 days/week. The only pretreatment demographic or clinical measure on which the groups differed significantly was age: placebo patients were approximately 3.5 yr older than topiramate patients. We included age as a factor in analyses, as described below. There were site differences on demographics: patients from Connecticut were predominantly European American (97%), whereas in Philadelphia there were fewer European Americans (77%) and more African Americans (18%) [$\chi^2_{(3)}$=14.60, p=0.002]. In addition, Connecticut patients were significantly [$\chi^2_{(1)}$=7.36, p=0.007] more likely to be married (71%) than Philadelphia patients (48%) and to work fulltime [78% vs. 48%, $\chi^2_{(2)}$=13.38, p=0.001]. We examined site as a factor in the analyses, as described below.

Heavy drinking days (Figure 1): There was a significant main effect of medication group, with topiramate patients reducing heavy drinking more than placebo patients [$F_{(1,1399)}$=23.37, p<0.001], and an interaction of medication group and treatment week [$F_{(1,1399)}$=19.91, p<0.0001], with topiramate patients decreasing heavy drinking more quickly than placebo patients. By the last week of treatment, the odds of experiencing a heavy drinking day in the placebo group was 5.33 (95%CI=1.68-7.28) times that of the topiramate group.

The number of patients with no heavy drinking days during the last four weeks of treatment in the topiramate group (N=24, 35.8%) was more than double that in the placebo group (N=12, 16.9%) [odds ratio=2.75 (95%CI=1.24-6.10)].

Abstinent days (Figure 2): There was a main effect of medication group [$F_{(1,1398)}$=4.63, p=0.032), with topiramate patients reporting more abstinent days than placebo patients. There was also a significant interaction of medication group and treatment week [$F_{(1,1398)}$=6.26, p=0.013): topiramate patients increased the number of abstinent days per week more rapidly than placebo patients. By the last week of treatment, the odds of abstaining from drinking in the topiramate group was 2.57 (95%CI=1.13-5.84) times that of the placebo group.

γ-glutamyltranspeptidase concentrations: There was a significant medication group by time interaction [$F_{(2,241)}$=3.44, p=0.034): topiramate-treated patients had a significantly greater decline in γ-glutamyltranspeptidase concentrations than placebo patients. Although concentrations were equivalent at baseline [topiramate: n=67, mean=65.9 (SD=91.5), placebo: n=71, mean=56.1 (SD=71.6)], there was a near-significant difference at midpoint [topiramate: n=59, mean=37.6 (SD=36.7), placebo: n=64, mean=50.1 (SD=64.8), p=0.060], and a significant difference at endpoint [topiramate: n=58, mean=36.3 (SD=40.2), placebo: n=63, mean=47.9 (SD=52.1), p=0.013].

Short Index of Problems score: Controlling for baseline scores, there was a significant difference in Short Index of Problems scores at study endpoint [Δ=7.9 for topiramate, from 14.9 (SD=8.6) at randomization to 7.0 (SD=7.2) at endpoint, and Δ=4.4 for placebo, declining from 15.5 (6.7) at randomization to 11.1 (SD=7.5) at endpoint; $F_{(1,128)}$=11.42, p=0.001].

Moderation of the Effects of Topiramate by rs2832407

Table S1 shows the demographic and pretreatment clinical features as a function of both genotype and treatment groups for the European-American subsample that was the focus of the pharmacogenetic analyses. Consistent with the finding in the intent-to-treat sample, placebo-treated patients were significantly older than topiramate-treated patients. No other demographic or clinical features differed significantly among the groups.

Heavy drinking days: There was a significant medication group by genotype interaction [$F_{(2,1227)}$=5.50, p=0.004] on heavy drinking days. As shown in Figure 3, topiramate was efficacious only in patients with the CC genotype. In follow-up comparisons in patients with the CC genotype, topiramate reduced heavy drinking days significantly more than placebo [$F_{(1,1228)}$=23.81, p<0.001], whereas in A-allele carriers, the difference between topiramate and placebo was not significant [$F_{(1,1228)}$=0.81, p=0.37].

Abstinent Days: For abstinent days, the interaction of medication group by the genotype group was not statistically significant [$F_{(2,1228)}$ = 1.36, p=0.26]. Nonetheless, as with heavy drinking days, the effect of topiramate appeared to be limited to the C-allele homozygotes (Figure 4) and a contrast between topiramate and placebo within C-allele homozygotes (compared with A-allele carriers) was significant [$F_{(1,1228)}$=4.08, p=0.044].

Impact of age, site differences, antidepressant treatment, and missing data: Age, treatment site, and antidepressant treatment were not associated with the drinking outcomes and including them in the model did not substantially alter the findings. Further, analyses based on multiple imputation of missing data yielded findings that were wholly consistent with the primary analyses.

Adverse Effects

Topiramate patients reported significantly more adverse events (mean=5.5, SD=3.1) than placebo patients [mean=3.0, SD=2.5; $F_{(1,135)}$=29.0, p<0.001]. Although approximately two-thirds of the adverse events were rated as mild, topiramate patients reported more moderate or severe events (mean=1.8, SD=1.3) than placebo patients (mean=0.4, SD=0.7)

[$F_{(1,135)}$=62.2, p<0.001]. Supplemental Table S2 lists the adverse events that occurred in at least 10% of the patients and the number of patients from each group that experienced the event. A significantly greater number of topiramate patients reported numbness/tingling, change in taste, loss of appetite, weight loss, difficulty concentrating, and difficulty with memory; these are all adverse effects that have been associated commonly with topiramate treatment (9,10).

Discussion

In this study, we examined the efficacy of topiramate at a maximal daily dosage of 200 mg in patients whose goal was to reduce their drinking, rather than to become abstinent from alcohol. We found significantly greater effects of topiramate than placebo in reducing heavy drinking days and increasing abstinent days. Both γ-glutamyltranspeptidase concentration, an objective measure of heavy drinking, and Short Index of Problems score, a measure of alcohol-related problems, were consistent with the self-reported drinking data. This evidence of efficacy compares favorably with the findings from two studies of topiramate that compared topiramate 300 mg with placebo to promote abstinence (9, 10). Further, the findings reported here are consistent with those of a study of non-treatment-seeking heavy drinkers, in which both 200 mg and 300 mg of topiramate reduced the frequency of heavy drinking more than placebo (11).

Of particular note, we observed that rs2832407, a non-coding intronic SNP in *GRIK1*, moderated topiramate's effects on heavy drinking days. Although a similar pharmacogenetic effect was seen for the number of abstinent days, it did not reach statistical significance. A larger sample could yield a significant moderator effect on this outcome as well. In a prior analysis of moderation by this SNP (19), patients with the CC genotype had lower plasma concentrations of topiramate and fewer adverse effects of the medication than A-allele carriers. We did not measure topiramate plasma concentrations, but found no effect of rs2832407on adverse effects produced by topiramate (see Supplemental Materials).

Although the functional effects of rs2832407 are unknown, the SNP is located 800 bp upstream of a *GRIK1* antisense transcript that overlaps with exon 8. Analysis of data from the 1000 Genomes Project (30) shows that it is in near-complete linkage disequilibrium (r^2=0.99) with rs363431, which maps to an antisense transcript in *GRIK1*. Further, ENCODE data show that rs2832407, which reflects a C-to-A substitution, lies within a CpG island (31). Thus, one possible mechanism for the observed moderating effect of rs2832407 is that the allele, or another *GRIK1* variant that is linked to it, affects the level of *GRIK1* mRNA or antisense RNA, reducing the effect of topiramate at GluK1-containing kainate receptors.

The high rate of treatment completion was a strength of this study. In contrast to the multicenter study by Johnson et al. (10), in which a significantly larger proportion of topiramate-treated patients than placebo patients discontinued treatment prematurely, we found no evidence of differential attrition. The observed reduction in heavy drinking days, particularly in patients with the CC genotype at rs2832407, to less, on average, than one heavy drinking day/week, is clinically important, as the frequency of heavy drinking is

correlated with a variety of alcohol-related negative consequences (32-34). In addition to requiring replication in a larger sample, the effects of topiramate and the moderating effects of rs2832407 require evaluation in populations other than European Americans. Together, these efforts will help to personalize the pharmacological treatment of heavy drinking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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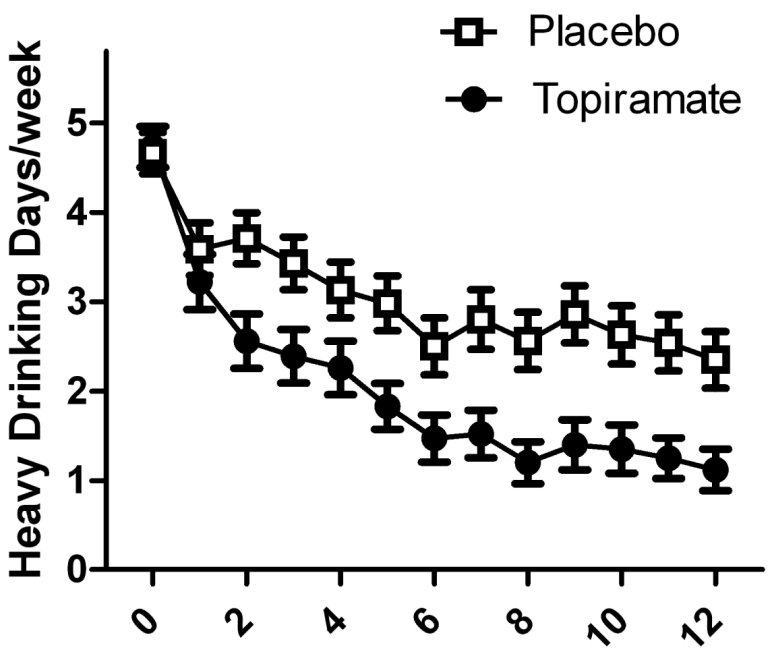

Figure 1.

Mean (SEM) Heavy Drinking Days per Week by Medication Group. Significant main effect of medication group ($F_{1,1399}$=23.37, p<0.001) and interaction of medication group by treatment week ($F_{1,1399}$=19.91, p<0.0001).

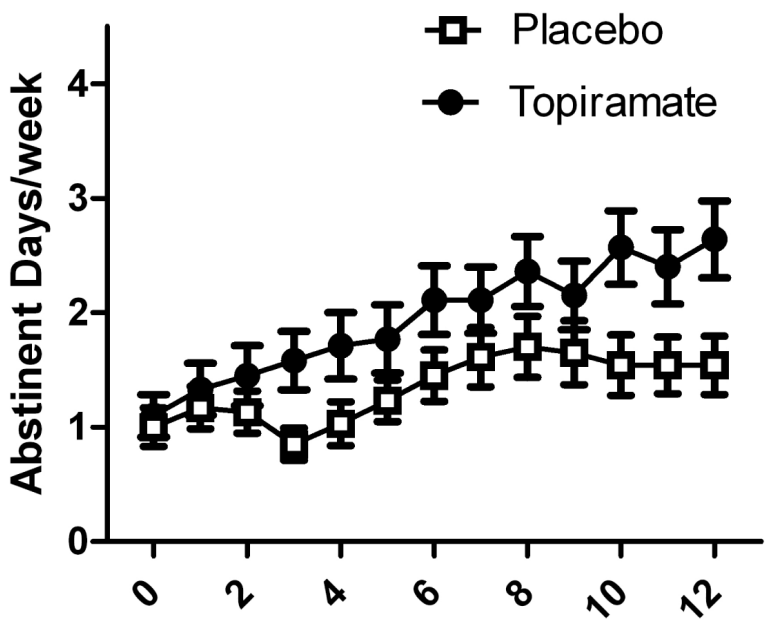

Figure 2.

Mean (SEM) Abstinent Days per Week by Medication Group. There was a significant main effect of medication group ($F_{1,1398}$=4.63, p=0.032) and interaction of medication group by treatment week ($F_{1,1398}$=6.26, p=0.013).

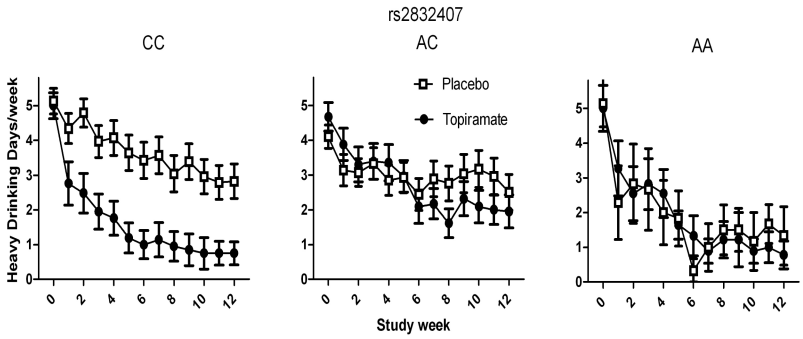

Figure 3.

Mean (SEM) Heavy Drinking Days per Week by Medication Group and rs2832407 Genotype. There was a significant medication group by genotype interaction ($F_{2,1227}$=5.50, p=0.004).

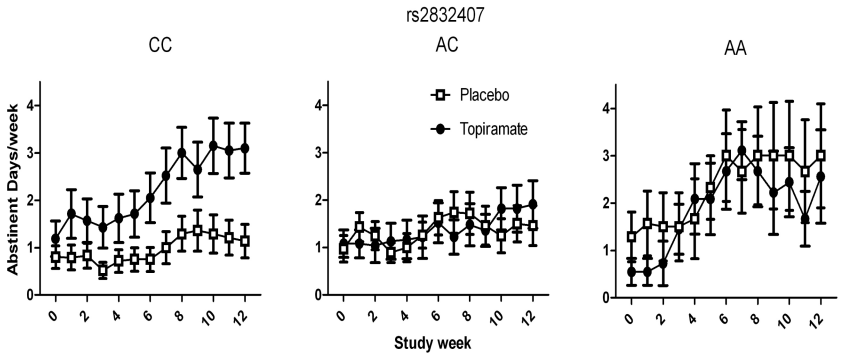

Figure 4.

Mean (SEM) Abstinent Days per Week by Medication Group and rs2832407 Genotype. The interaction of medication group by genotype group was not statistically significant ($F_{2,1228} = 1.36$, p=0.26).

Table 1

Baseline Features by Genotype and Treatment Assignment for Caucasians (n=122)

Genotype Group (rs2832407)	**CC (42%)[a]**		**AC (43%)[a]**		**AA (15%)[a]**	
Medication Group	**Topiramate (n=21)**	**Placebo (n=30)**	**Topiramate (n=24)**	**Placebo (n=29)**	**Topiramate (n=ll)**	**Placebo (n=7)**
Demographics						
Sex (Male)	71.4%	46.7%	66.7%	62.1%	54.5%	85.7%
Age (yr)[b]	51.7 (8.3)	52.5 (6.4)	49.8 (6.8)	53.0 (8.2)	50.6 (6.7)	56.3 (7.2)
Married	66.7%	66.7%	66.7%	62.1%	63.6%	85.7%
Education (yr)	15.7 (2.4)	15.0 (2.2)	15.9 (1.9)	15.1 (2.8)	15.0 (2.4)	15.9 (1.5)
Clinical Measures						
Lifetime Major Depression	23.8%	36.7%	20.8%	24.1%	27.3%	28.6%
Beck Depression Inventory score	7.4(5.1)	6.8(5.1)	5.1 (3.9)	7.1 (5.4)	4.9(3.3)	5.4 (4.6)
Short Index of Problems score	14.5 (8.0)	15.4(6.5)	14.5 (9.9)	15.6(7.2)	16.6 (7.2)	12.6(5.1)
90-day pretreatment drinking[c]						
Percent Days Abstinent	0.12 (0.14)	0.07 (0.11)	0.13 (0.17)	0.13 (0.15)	0.07 (0.08)	0.19 (0.17)
Percent Heavy Drinking Days	0.70 (0.25)	0.72 (0.27)	0.66 (0.28)	0.58 (0.25)	0.70 (0.32)	0.74 (0.25)

[a] The genotype frequencies in European Americans were in Hardy-Weinberg Equilibrium [$\chi^2_{(2)}$= 0.61, p=0.74]

[b] p=0.040 for main effect of treatment assignment (means are 50.7 yr for topiramate and 53.1 yr for placebo)

[c] Preceding the screening visit.