Topiramate for Treating Alcohol Dependence
A Randomized Controlled Trial

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Context Hypothetically, topiramate can improve drinking outcomes among alcohol-dependent individuals by reducing alcohol's reinforcing effects through facilitation of γ-aminobutyric acid function and inhibition of glutaminergic pathways in the corticomesolimbic system.

Objective To determine if topiramate is a safe and efficacious treatment for alcohol dependence.

Design, Setting, and Participants Double-blind, randomized, placebo-controlled, 14-week trial of 371 men and women aged 18 to 65 years diagnosed with alcohol dependence, conducted between January 27, 2004, and August 4, 2006, at 17 US sites.

Interventions Up to 300 mg/d of topiramate (n=183) or placebo (n=188), along with a weekly compliance enhancement intervention.

Main Outcome Measures Primary efficacy variable was self-reported percentage of heavy drinking days. Secondary outcomes included other self-reported drinking measures (percentage of days abstinent and drinks per drinking day) along with the laboratory measure of alcohol consumption (plasma γ-glutamyltransferase).

Results Treating all dropouts as relapse to baseline, topiramate was more efficacious than placebo at reducing the percentage of heavy drinking days from baseline to week 14 (mean difference, 8.44%; 95% confidence interval, 3.07%-13.80%; $P=.002$). Prespecified mixed-model analysis also showed that topiramate compared with placebo decreased the percentage of heavy drinking days (mean difference, 16.19%; 95% confidence interval, 10.79%-21.60%; $P<.001$) and all other drinking outcomes ($P<.001$ for all comparisons). Adverse events that were more common with topiramate vs placebo, respectively, included paresthesia (50.8% vs 10.6%), taste perversion (23.0% vs 4.8%), anorexia (19.7% vs 6.9%), and difficulty with concentration (14.8% vs 3.2%).

Conclusion Topiramate is a promising treatment for alcohol dependence.

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HYPOTHETICALLY, TOPIRAMATE, a sulfamate-substituted fructopyranose derivative, can decrease alcohol reinforcement and the propensity to drink.[1] Topiramate might accomplish this by reducing corticomesolimbic dopamine release through at least 2 principal pharmacological processes. These include the facilitation of γ-aminobutyric acid function through a nonbenzodiazepine site on the γ-aminobutyric acid-A receptor[2] and the antagonism of glutamate activity at α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate receptors.[1]

Initial evidence that topiramate can improve the drinking outcomes of alcohol-dependent individuals comes from an earlier, single-site, double-blind, randomized controlled trial with a different design and a shorter duration.[3]

Now, in a multisite, 14-week, randomized controlled trial, we sought to determine the efficacy of topiramate (up to 300 mg/d) compared with placebo

For editorial comment see p 1691.

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as a treatment for alcohol-dependent individuals receiving weekly manual-guided Brief Behavioral Compliance Enhancement Treatment (BBCET) to promote adherence with the study medication and the treatment regimen.

METHODS

Participants

We enrolled 371 men and women diagnosed with alcohol dependence according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*),[4] using the *Structured Clinical Interview* for the *DSM-IV*.[5]

Participants were recruited at 17 sites in the United States between January 27, 2004, and August 4, 2006, by newspaper, radio, and television advertisements.

We included participants aged 18 to 65 years who drank 35 or more (men) and 28 or more (women) standard drinks per week, as measured by timeline follow-back,[6] during the 28-day period preceding the screening visit to assess study eligibility and during the 7-day period between the screening visit and randomization. A standard drink was 0.5 oz of absolute alcohol, equivalent to 10 oz of beer, 4 oz of wine, or 1 oz of 100-proof liquor.[7] Participants had to (1) score 8 or higher on the Alcohol Use Disorders Identification Test,[8] which assessed the personal and social harm after alcohol consumption; (2) have a body mass index (BMI) higher than 18 (calculated as weight in kilograms divided by height in meters squared); and (3) have a negative urine toxicological screening result for opioids, cocaine, amphetamines, antidepressants, propoxyphenes, and barbiturates at the time of randomization and before the beginning of the double-blind period in week 0. Participants with a positive urine drug screening result for tetrahydrocannabinol or benzodiazepines in the week prior to randomization (week –1) could be enrolled if they had a negative urine drug screen on retesting 7 days later and met all other enrollment criteria. Although all participants were currently drinking at enrollment, to be enrolled they had to express a desire to stop or reduce their consumption of alcohol, with the possible long-term goal of abstinence.

We excluded participants who (1) had a current Axis I psychiatric diagnosis on the *DSM-IV* other than alcohol, nicotine, or caffeine dependence; (2) had a history in the last 6 months of substance abuse or dependence excluding dependence on alcohol, nicotine, or caffeine; (3) had clinically significant alcohol withdrawal symptoms (revised Clinical Institute Withdrawal Assessment for Alcohol scale [CIWA-Ar][9] score >10); (4) had made more than 4 unsuccessful formal inpatient treatment attempts to curb alcohol dependence; (5) had received formal psychotherapy for a psychiatric disorder other than alcohol dependence within 3 months before the enrollment visit; (6) were taking antipsychotics, antiepileptics, mood stabilizers, carbonic anhydrase inhibitors, opioid analgesics, or systemic steroids at the enrollment visit (a washout period, depending on the pharmacokinetic profile of the medication[s], was allowed); (7) had clinically significant depression, which was defined as a score higher than 24 on the Montgomery-Asberg Depression Rating Scale (MADRS)[10] or based on the impression of a study physician; (8) had suicidal ideation within 30 days of week 0, as verified by medical history or a score higher than 4 on item 10 (suicidal thoughts) of the MADRS, or had attempted suicide during the same period; (9) were receiving treatment for alcohol dependence other than Alcoholics Anonymous; (10) had clinically significant medical condition(s) (ie, on physical examination, electrocardiogram recording, hematological assessment, biochemistry including bilirubin concentration, and urinalysis); (11) had a history of or current renal impairment (ie, creatinine clearance $\leq$60 mL/min), renal stones, seizures, or unstable hypertension; (12) had progressive neurodegenerative disorders or clinically significant neurological disorders including seizures; (13) were pregnant or lactating; (14) were taking medications that could affect alcohol consumption or a carbonic anhydrase inhibitor; (15) had been compelled to receive treatment for alcohol dependence to avoid imprisonment, parole, probation, or loss of employment; or (16) were from the same household as another study participant.

Approval for this study was provided by the institutional review boards of all 17 participating sites, and participants provided written informed consent.

Assessments

We assessed participants at screening (the beginning of week –1; approximately 7 days before randomization) on (1) medical eligibility to meet study inclusion criteria; (2) drinking characteristics for the previous 28 days using timeline follow-back; (3) depressed mood using the MADRS; (4) breath alcohol concentration; and (5) concomitant medications. A diary card for recording alcohol consumption also was distributed to the participants at this time. Participants returned for a separate visit at the end of week –1 to complete the screening process, which included assessment of (1) physical health (via physical examination, electrocardiogram, vital signs [ie, blood pressure, pulse, and BMI], hematological and biochemical screenings, urine tests [including urine drug screening], and a urine pregnancy test for women with childbearing potential); (2) withdrawal symptoms (CIWA-Ar); (3) depressed mood (MADRS); (4) personal and psychosocial harm from alcohol (Alcohol Use Disorders Identification Test); (5) concomitant medications; (6) adverse events; and (7) breath alcohol concentration. Participants were not allowed to provide written informed consent unless they had a breath alcohol concentration of less than 0.02%.

During the double-blind period from weeks 0 to 14, participants were assessed weekly on measures of drinking (measured by timeline follow-back using a diary card as a memory guide); vital

Table 1. Topiramate Dose-Escalation Schedule[a]

Weeks[b]	AM Tablet Dose, mg	No. of Tablets	PM Tablet Dose, mg	No. of Tablets	Total Daily Dose, mg	Total No. of Tablets
0-1	0	0	25	1	25	1
1-2	25	1	25	1	50	2
2-3	25	2	25	2	100	4
3-4	25	3	25	3	150	6
4-5	100	1	100	1	200	2
5-14	100	1	100	2	300	3

[a]The placebo and topiramate groups received the same number of tablets; placebo tablets were inactive.
[b]Weeks represent the beginning of 1 week to the beginning of the next. Study end was the beginning of week 14.

signs (including BMI); alcohol withdrawal symptoms using the CIWA-Ar; concomitant medications; medication adherence (ie, [tablets dispensed – tablets returned]/total tablets prescribed); adverse events; and breath alcohol concentration. Participants were not allowed to complete assessments during the double-blind period unless they had a breath alcohol concentration of less than 0.04%. At each weekly visit during weeks 0, 4, 8, 12, and 14, we assessed serum topiramate level and plasma level of the liver enzyme γ-glutamyltransferase (GGT).[11] Plasma GGT was used as the biomarker to provide a laboratory measure of drinking reduction because it is accepted widely, is validated, and is commensurate with the reporting in the previous single-site trial.[3] It was chosen because measurement of the other common biomarker (carbohydrate-deficient transferrin) could be confounded by the expected topiramate-induced weight loss. Hematological and biochemical screenings including urine pregnancy tests were repeated at weeks 0, 4, 8, 10, 12, and 14. Depression was measured using the MADRS every 2 weeks from weeks 0 to 14.

Participants classified their race according to 4 choices: white, black, Asian, or other. This information was collected to allow comparison with other studies regarding racial diversity within the sample. No analyses by race were planned or conducted.

Procedures

Participants continuing to meet drinking eligibility criteria after the 7-day screening period were randomized in a 1:1 ratio to topiramate or placebo according to a computer-generated code. Randomization was balanced using permuted blocks. The participants and the investigators were blinded to the treatment assignment. To maintain the blind, sealed envelopes containing study medication identification were provided to the investigators, who were instructed that this envelope could only be opened if specific emergency treatment would be dictated by knowing the participants' treatment assignment. Permission also had to be obtained from the sponsor before opening the envelope. No such incident occurred.

Study medication was dispensed in a double-blind fashion for the efficacy determination period, which began at the beginning of week 0 and finished at the beginning of week 14. The medication dose was titrated from the beginning of week 0 to the end of week 5 (ie, the beginning of week 6) and maintained from the end of week 5 to the beginning of week 14. Titration was achieved by scheduled increments in the number of topiramate tablets or an equivalent number of matching placebo tablets (TABLE 1). Participants had to achieve a minimum topiramate dose of 50 mg/d or the placebo equivalent to remain in the trial. From weeks 14 to 16, participants were tapered off their study medication as a safety precaution. Topiramate and matching placebo tablets were provided by Ortho-McNeil Janssen Scientific Affairs LLC (Raritan, New Jersey).

All participants received the BBCET as their psychosocial treatment. A standardized, brief (ie, delivered in about 15 minutes), psychosocial adherence enhancement procedure, the BBCET emphasized that medication adherence was crucial to changing participants' drinking behavior. Brief interventions,[12] such as the BBCET, have been shown to benefit the treatment of alcohol dependence. The BBCET was modeled on the clinical management condition in the National Institute of Mental Health collaborative depression trial, which was used as an adjunct to the medication condition for that study.[13] Also, the BBCET was used successfully as the psychosocial treatment platform in the previous efficacy trial of topiramate for treating alcohol dependence.[3] Trained clinicians, including nurse practitioners, delivered manual-guided BBCET during each week of the double-blind period. Uniformity and consistency of the BBCET delivery were ensured by training and ongoing supervision, including evaluation of a random selection of about 10% of audiotaped sessions at all sites by the study BBCET supervisor (N.A-D.). The BBCET manual can be obtained from the lead investigator (B.A.J.) or the book that contains it.[14]

Outcome and Safety Measures

The primary efficacy variable was the percentage of heavy drinking days (number of days for which men consumed ≥5 standard drinks per day and women consumed ≥4 standard drinks per day divided by the number of study days).

Secondary outcome measures included other self-reported measures of drinking (percentage of days abstinent; calculated as the number of nondrinking days divided by the number of study days); drinks per drinking day

(average of 14 weekly drinks per drinking day ratios; defined as the number of drinks consumed during a given week divided by the number of drinking days for that week); and the laboratory measure of alcohol consumption (plasma GGT).

We assessed safety using vital signs (ie, blood pressure, pulse, temperature, and BMI), hematological and biochemical tests (including liver function tests [ie, aspartate aminotransferase and alanine aminotransferase], bicarbonate, and pH level), depressed mood (MADRS), withdrawal symptoms (CIWA-Ar), concomitant medications, adherence with taking medication, dose-serum topiramate level concordance (ie, relationship between assigned dose of topiramate and its serum level), retention, breath alcohol concentration, and adverse events.

An independent data monitoring committee met periodically to ensure participants' safety.

Power Calculations

We estimated statistical power for this study based on data from a previous 12-week, double-blind, single-center trial in which there was a significant reduction in the percentage of heavy drinking days for topiramate vs placebo (mean [SD], 42.9% [28.2%] vs 31.4% [25.2%], respectively).[3]

To be conservative, the larger SD was used in the sample size calculation. Furthermore, it was anticipated that this multicenter study would have more variability than the previous single-center trial. Thus, the SD used in the sample size calculation was increased by 20% from 28.2% to 33.9%. Based on a 2-sample *t* test, we determined that a sample size of 184 participants for the topiramate and placebo groups (ie, a total of 368 participants) would be needed to achieve 90% power to detect a mean group difference of 11.5% in percentage of heavy drinking days at a 2-sided significance level of .05.

Statistical Analysis Plan

General Approaches. We managed data according to the International Conference on Harmonisation guidelines of good clinical practice. Individual plots were checked for unusual values and completeness. Efficacy values were validated as correct against case records. Inferential comparisons were provided for the response averaged across the entire double-blind phase unless stated otherwise. For all statistical tests, differences between treatment groups were accepted as significant if they achieved the .05 level with 2-tailed tests. For the primary analysis, inferential testing was conducted on all randomized participants. For all prespecified analyses, inferential testing was conducted on all randomized participants returning for at least 1 double-blind visit and receiving at least 1 medication dose. Data were analyzed with SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

The duration of the double-blind phase (ie, weeks 0-14) was calculated as the date of the first double-blind dose plus 1 day to the date when the last double-blind dose of medication was taken but before the 2-week period during which participants were tapered off the study medication.

Analysis of the Outcome and Safety Measures. The null hypothesis for the primary efficacy variable was that there would be no difference between topiramate and placebo in average percentage of heavy drinking days during the double-blind phase. For the primary analysis, we tested the null hypothesis on the percentage of heavy drinking days in all randomized participants by imputing data for all dropouts as relapse to the baseline measure (ie, data from the 7-day period prior to taking the first dose of medication at week 0). This primary analytic model was done to provide the most conservative estimate for the difference in treatment effect between topiramate and placebo. We also tested this null hypothesis in all randomized participants who took at least 1 study medication dose and had at least 1 double-blind visit, without imputing missing data for dropouts (prespecified analysis). For both approaches, we analyzed the percentage of heavy drinking days using a repeated-measures model with treatment group, center, week, sex, baseline percentage of heavy drinking days, chronological age, age at onset of problem drinking, and treatment × week interaction as covariates. An unstructured covariance matrix was used to model the correlations between repeated measurements within participants. Least-square means and their 95% confidence intervals (CIs) were derived for each treatment group; 95% CIs were calculated for the difference in least-square means between treatment groups.

An independent statistician validated the data analysis for the outcome measures. The independent statistician also tested the null hypothesis for the primary efficacy variable (ie, percentage of heavy drinking days) using the inverse-probability weighting method[15] to determine whether the repeated-measures mixed model accounted adequately for the differential attrition rate between the topiramate and placebo groups. In this method, participants' data were weighted by the inverse probability of their completing the double-blind phase. These predictions, based on a hazard model for dropout at each week, were assumed to depend on factors collected prior to that week. Specifically, our model depended on treatment group, center, chronological age, age at onset of problem drinking, sex, percentage of heavy drinking days in the previous week and its interaction with treatment, and the average number of central nervous system adverse events in the preceding week.

We used a fixed-sequence multiple testing procedure to control for type I error when determining the earliest time point at which the difference between the 2 groups' percentage of heavy drinking days became statistically significant and was sustained for subsequent time points. Because the primary analytic approach imputes all missing data with the baseline value to provide a complete data set, we used an analysis of covariance model to test the between-groups difference. The

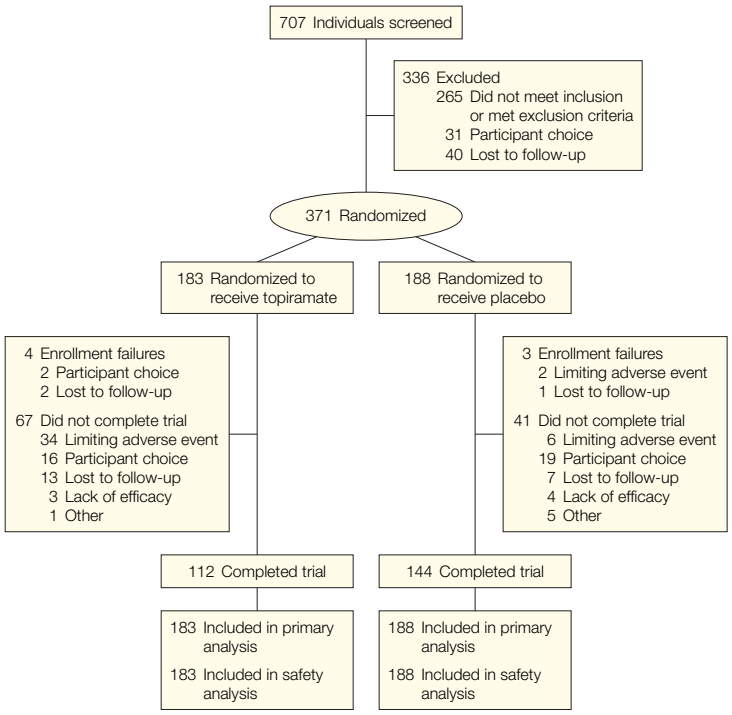
procedure was used to test the difference between the 2 groups' percentage of heavy drinking days at week 14 at the .05 significance level (2-tailed). If there was a significant difference at week 14, this procedure would be repeated for the preceding weeks until a time point was reached at which there was no difference. A finding of no significant difference at week 14 would have stopped the comparison for the preceding weeks.

Secondary self-reported drinking data and plasma GGT were analyzed to provide a more complete picture of drinking outcomes. Secondary self-reported measures of drinking (ie, percentage of days abstinent and drinks per drinking day) were analyzed similarly to the primary efficacy variable. Plasma GGT was analyzed as its incremental log ratio over time, as in the previous study.[3] All analyses were conducted using both the method of imputing missing data with the baseline value (ie, the primary analytic approach) and the prespecified repeated-measures mixed model, which did not impute missing data.

We estimated the hazard ratio (HR) of achieving 28 or more days of continuous abstinence and 28 or more days of continuous nonheavy drinking using the Cox proportional hazards model. Candidate covariates for the Cox proportional hazards model were the same as those used for the repeated-measures analysis. Further, using the Kaplan-Meier method, we calculated the cumulative probability function of reaching 28 or more days of continuous abstinence and 28 or more days of continuous nonheavy drinking for the topiramate and placebo groups. We compared the cumulative probability functions using the log-rank test. All analyses were conducted using both the method of imputing missing data with the baseline value (ie, the primary analytic approach) and the prespecified analysis, which did not impute missing data.

We compared the difference in scores on the safety measures between the topiramate and placebo groups, except for the dose-serum topiramate concordance, using a simple 2-group repeated-measures model. In contrast, the topiramate dose-serum concordance level was analyzed by regression analysis, and a relationship between serum topiramate level and the percentage of heavy drinking days for those who completed week 14 was examined using a Pearson correlation. Descriptive data from the safety measures are reported qualitatively.

Figure 1. Trial Profile



Trial completers were participants who completed all 14 weeks of double-blind treatment. Enrollment failures were those who received medication at the beginning of week 1 but did not return to the clinic for further assessment.

Type I Error Rate. We tested between-treatment differences on a number of self-reported drinking measures and the laboratory drinking measure. Based on the consideration that these measures were correlated highly, we expected little inflation of the family-wise type I error rate. In fact, the Pearson correlation between the primary efficacy measure, percentage of heavy drinking days, and the other self-reported drinking measures (drinks per drinking day and percentage of days abstinent) ranged from 0.65 to 0.85 ($P<.001$). The bivariate correlations of percentage of heavy drinking days and other self-reported drinking measures were estimated using baseline data. As described previously, when testing between-treatment differences over time within each measure, we applied a fixed-sequence multiple testing procedure to control the family-wise type I error rate.

Of note, between-treatment differences on any of the above measures remained highly significant even when we applied the Hochberg step-up multiple testing procedure to control the family-wise type I error rate, with the very conservative assumption that these measures were independent.

RESULTS

We randomized 183 participants into the topiramate group and 188 participants into the placebo group (N=371; FIGURE 1). Participants in the 2 groups

had similar baseline characteristics (TABLE 2).

For the primary analysis of percentage of heavy drinking days, when imputing data for all dropouts as relapse to baseline measure, topiramate compared with placebo recipients showed greater lowering of percentage of heavy drinking days from baseline to week 14 (ie, from a mean [SD] of 81.91% [20.04%] to 43.81% [40.43%] for topiramate vs 81.97% [19.92%] to 51.76% [37.43%] for placebo; mean difference, 8.44% [95% CI, 3.07%-13.80%]; $P=.002$). The difference between the groups occurred in week 4 (FIGURE 2A). Also, on the secondary measures of self-reported drinking and the laboratory marker of drinking, using the primary analytic method of imputing all dropouts as relapse to baseline, topiramate was more efficacious than placebo (TABLE 3).

For the prespecified analysis of percentage of heavy drinking days, without imputing missing data for dropouts, topiramate was more efficacious than placebo at improving the percentage of heavy drinking days (mean difference, 16.19% [95% CI, 10.79%-21.60%]; $P<.001$). The difference between the groups occurred in week 2 (Figure 2B). Also, on the secondary measures of self-reported drinking and the laboratory marker of drinking, using the prespecified analysis, topiramate was superior to placebo (Table 3).

Table 2. Baseline Demographics and Psychopathological Characteristics

	No. (%) of Participants[a]	
	Topiramate (n = 179)	Placebo (n = 185)
Age, mean (SD), y	46.7 (9.4)	47.8 (8.7)
Sex		
Male	133 (74.3)	133 (71.9)
Female	46 (25.7)	52 (28.1)
Race/ethnicity		
White	152 (84.9)	157 (84.9)
Black	12 (6.7)	16 (8.6)
Asian	1 (0.6)	2 (1.1)
Other[b]	14 (7.8)	10 (5.4)
Self-reported alcohol drinking, mean (SD)[c]		
Heavy drinking days, %	82.35 (19.56)	83.82 (19.36)
Days abstinent, %	10.91 (16.03)	9.71 (14.99)
Drinks/drinking day	11.42 (4.82)	10.87 (4.34)
Breath alcohol concentration, mean (SD), %	0.002 (0.006)	0.002 (0.008)
CIWA-Ar score, mean (SD)	1.55 (2.09)	1.38 (1.93)
Age of alcoholism onset, mean (SD), y	32.7 (11.8)	34.4 (10.8)
Alcohol counseling	9 (5.0)	5 (2.7)
No. of previous inpatient treatment stays		
0	148 (82.7)	164 (88.6)
1	16 (8.9)	13 (7.0)
2	9 (5.0)	6 (3.2)
3	5 (2.8)	2 (1.1)
4	1 (0.6)	0
Beverage of choice		
Carbonated	71 (39.7)	73 (39.5)
Noncarbonated	86 (48.0)	85 (45.9)
No preference	22 (12.3)	27 (14.6)

Abbreviation: CIWA-Ar, revised Clinical Institute Withdrawal Assessment for Alcohol scale.
[a] Unless otherwise indicated.
[b] Participants who selected "other" were asked to specify further. Of the 14 in the topiramate group, 13 self-identified as Hispanic and 1 as Cuban. Of the 10 in the placebo group, 8 self-identified as Hispanic, 1 as Spanish, and 1 as Native American.
[c] Reflects mean values during the 28-day period preceding the screening visit (ie, the beginning of week −1). All other values refer to baseline (ie, week 0).

The inverse-weighting method performed by the independent statistician on the primary efficacy variable (ie, percentage of heavy drinking days) showed similar results (mean difference at week 14, 18.80% [95% CI, 10.38%-27.12%]; $P<.001$). Significant differences between the topiramate and placebo groups did, however, emerge earlier in week 2 for the prespecified mixed model compared with week 4 for the inverse-weighting method.

Compared with placebo recipients, topiramate recipients experienced significant reductions not only in self-reported drinking but also on plasma GGT ($P<.001$ for all comparisons; Table 3).

Using the primary analytic approach of imputing missing data with the baseline value, topiramate compared with placebo treatment was associated with a significantly higher rate of achieving 28 or more days of continuous nonheavy drinking (HR, 2.28 [95% CI, 1.44-3.59]; $P<.001$) and 28 or more days of continuous abstinence (HR, 5.03 [95% CI, 2.07-12.20]; $P<.001$).

Using the prespecified approach of not imputing missing data, topiramate compared with placebo treatment was associated with a significantly higher rate of achieving 28 or more days of continuous nonheavy drinking (HR, 2.79 [95% CI, 1.76-4.42]; $P<.001$) and 28 or more days of continuous abstinence (HR, 5.96 [95% CI, 2.46-14.46]; $P<.001$).

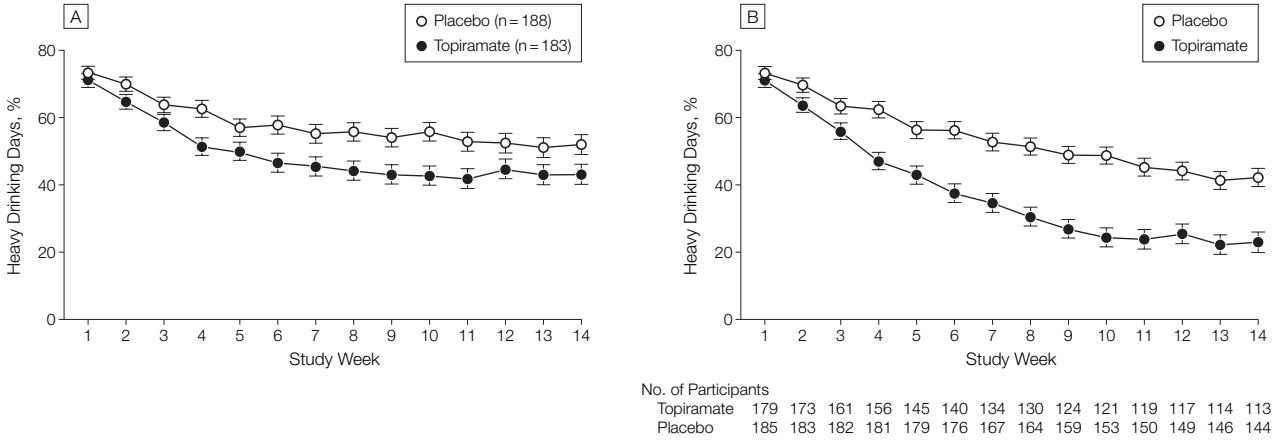
The Kaplan-Meier estimates of the cumulative probability function of achieving 28 or more days of continuous abstinence are presented in FIGURE 3A using imputed data and in Figure 3B using nonimputed data. With both approaches, the topiramate group reached 28 or more days of continuous abstinence significantly faster than the placebo group (log-rank $P<.001$ for both approaches).

The Kaplan-Meier estimates of the cumulative probability function of achieving 28 or more days of continuous nonheavy drinking are presented in FIGURE 4A using imputed data and in Figure 4B using nonimputed data.

With both approaches, the topiramate group reached 28 or more days of continuous nonheavy drinking significantly faster than the placebo group (log-rank $P<.001$ for both approaches).

In regard to safety measures at study end, the topiramate group compared with the placebo group was associated with reduced liver enzymes (mean difference for aspartate aminotransferase, 4.70 [95% CI, 1.86-7.54] and mean difference for alanine aminotransferase, 6.74 [95% CI, 2.99-10.49]) and decreased BMI (mean difference, 1.08 [95% CI, 0.81-1.34; $P<.001$). Although plasma bicarbonate levels were significantly lower for the topiramate group compared with the placebo group (mean difference, 2.50 mmol/L [95% CI, 1.89-3.11 mmol/L]; $P<.001$), this did not require any medical intervention. Plasma pH level did not differ signifi-

Figure 2. Percentage of Heavy Drinking Days From Study Week 1



Error bars indicate standard error. A, the primary analytic approach of imputing missing data with the baseline value is illustrated. The comparison between the participants taking placebo and topiramate became statistically significant at study week 4 ($P<.001$). B, the prespecified approach of not imputing missing data is illustrated; the data were analyzed using a repeated-measures mixed model. The comparison between the participants taking placebo and topiramate became statistically significant at study week 2 ($P=.04$).

Table 3. Difference Between Placebo and Topiramate on the Self-Reported Drinking Measures and the Laboratory Marker of Drinking

Outcome	Mean (SD) Difference[a]				Mean Difference Between Study Groups (95% CI)[b]	*P* Value
	Baseline (Week 0)		Study End (Week 14)			
	Topiramate (n = 183)	Placebo (n = 188)	Topiramate (n = 183)	Placebo (n = 188)		
Primary Analytic Model of Imputing the Baseline Value for All Dropouts						
Self-reported and laboratory drinking measures[c]						
Heavy drinking days, %	81.91 (20.04)	81.97 (19.92)	43.81 (40.43)	51.76 (37.43)	8.44 (3.07 to 13.80)	.002
Days abstinent, %	9.64 (15.94)	9.35 (16.43)	37.56 (39.66)	29.06 (32.35)	–7.68 (–12.49 to –2.87)	.002
Drinks/drinking day	11.04 (4.62)	10.90 (5.11)	6.53 (5.44)	7.46 (4.93)	0.88 (0.25 to 1.51)	.006
Log GGT ratio[d]	3.88 (0.81)	4.00 (0.85)	–0.05 (0.09)	–0.02 (0.09)	0.03 (0.01 to 0.04)	<.001
Prespecified Mixed Model Analytic Approach						
Self-reported and laboratory drinking measures[e]	(n = 179)	(n = 185)	(n = 113)	(n = 144)		
Heavy drinking days, %	82.09 (20.08)	81.82 (20.02)	20.00 (30.46)	42.44 (36.38)	16.19 (10.79 to 21.60)	<.001
Days abstinent, %	9.48 (15.98)	9.45 (16.53)	54.94 (40.10)	34.48 (33.89)	–13.39 (–18.65 to –8.14)	<.001
Drinks/drinking day	11.05 (4.62)	10.94 (5.14)	3.62 (3.66)	6.33 (4.45)	1.77 (1.19 to 2.36)	<.001
Log GGT ratio[d]	3.89 (0.80)	3.99 (0.84)	–0.09 (0.12)	–0.02 (0.10)	0.05 (0.03 to 0.07)	<.001

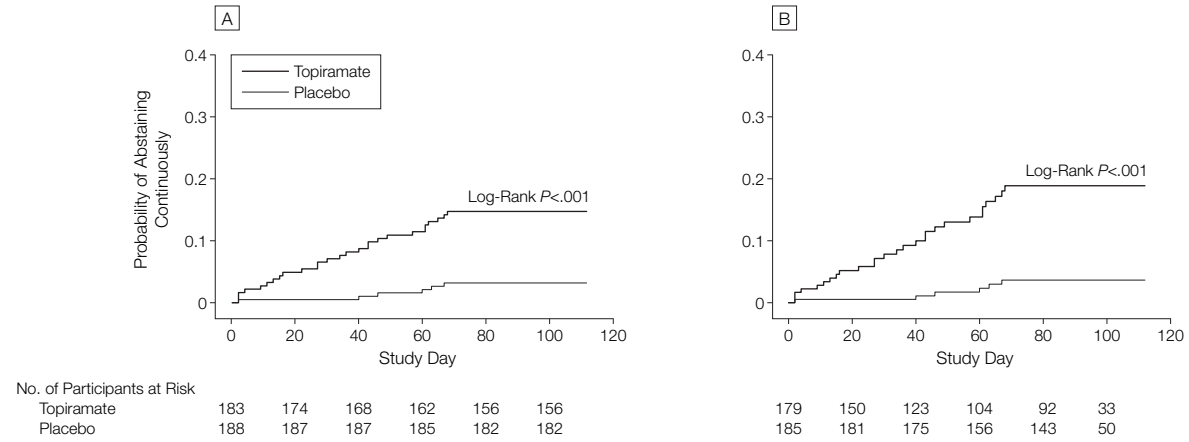
Abbreviations: CI, confidence intervals; GGT, γ-glutamyl transferase.
[a] The values provided are the unadjusted numbers.
[b] The values were calculated from least-square means for the difference in treatment effect between topiramate and placebo averaged across the entire double-blind period.
[c] The self-reported drinking data refer to values collected in the preceding week. One randomized placebo participant had missing data on all drinking outcomes. For this participant, the baseline drinking values were imputed as the average of the drinking values for all other randomized placebo participants. Three participants had missing data on baseline plasma GGT. For these participants, their baseline plasma GGT levels were imputed using the predicted values from the linear regression model derived from all other randomized participants. This model included treatment group, center, chronological age, age at onset of problem drinking, sex, and baseline percentage of heavy drinking days.
[d] Calculated and analyzed as previously reported.[3] The ratio was the (log GGT at a given time point – log GGT at baseline)/log GGT at baseline. At baseline, log GGT ratio is simply the logarithm of the GGT value. The more negative the value at study end, the greater the reduction from baseline.
[e] The self-reported drinking data refer to values collected in the preceding week.

cantly between the topiramate and placebo groups (data not shown). No other hematological or biochemical tests differed between the 2 groups (data not shown). The 2 groups did not differ on depressed mood (mean difference, 0.57 [95% CI, –0.13 to 1.26]; *P*=.11) or general mood (mean difference, 0.80 [95% CI, –2.52 to 4.12]; *P*=.63).

Generally, alcohol withdrawal scores assessed on the CIWA-Ar were exceedingly low and did not differ between the topiramate and placebo groups (mean difference, 0.01 [95% CI, –0.31 to 0.33]; *P*=.94). Few participants reported attending Alcoholics Anonymous meetings (5.0% for the topiramate group and 2.7% for the placebo group). Rates of concomitant medication use for the topiramate and placebo groups were 88% and 95.7%, respectively. The following percentages of participants received these topiramate doses or equivalent placebo doses, respectively, 0-25 mg (3.8%, 1.6%), 25-50 mg (8.2%, 0.5%), 50-100 mg (12%, 3.2%), 100-150 mg (10.4%, 6.9%), 150-200 mg (13.7%, 10.1%), and 200-300 mg (50.8%, 77.7%).

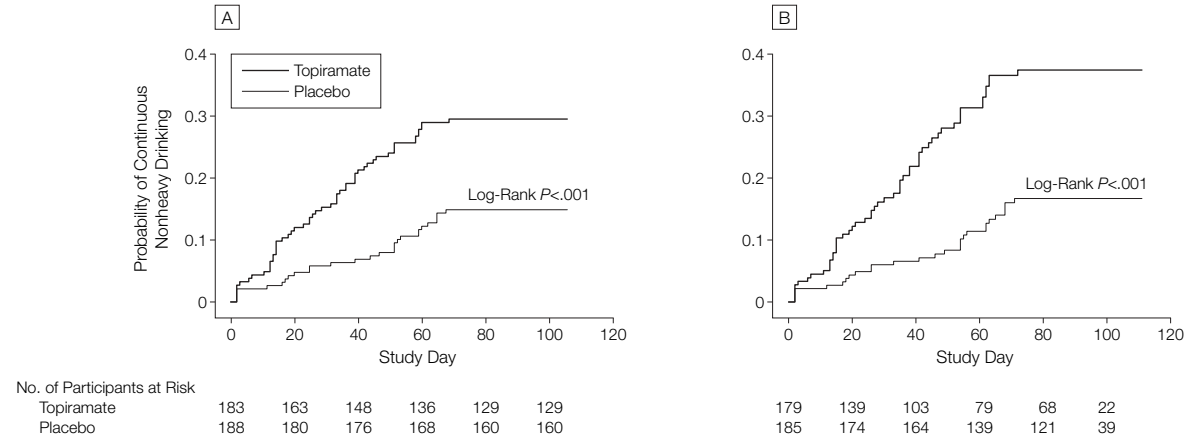
The rates for medication adherence were similar, at 91.46% (SD, 14.96%) for those taking topiramate compared with 90.09% (SD, 13.12%) for those taking placebo. The mean (SD) of the topiramate dose was 171.4 (107.6) mg

Figure 3. Time to First Day of 28 or More Days of Continuous Abstinence



A, The primary analytic approach of imputing missing data with the baseline value is illustrated; the observed numbers of participants in the topiramate group meeting this criterion were 27 of 183 compared with 6 of 188 in the placebo group. B, The prespecified approach of not imputing missing data is illustrated; the observed numbers of participants in the topiramate group meeting this criterion were 27 of 179 compared with 6 of 185 in the placebo group. The primary analysis did not have censored observations; in contrast, the prespecified analysis could have censored observation(s) at the week of dropout.

Figure 4. Time to First Day of 28 or More Days of Continuous Nonheavy Drinking



A, The primary analytic approach of imputing missing data with the baseline value is illustrated; the observed numbers of participants in the topiramate group meeting this criterion were 54 of 183 compared with 28 of 188 in the placebo group. B, The prespecified approach of not imputing missing data is illustrated; the observed numbers of participants in the topiramate group meeting this criterion were 54 of 179 compared with 28 of 185 in the placebo group. The primary analysis did not have censored observations; in contrast, the prespecified analysis could have censored observation(s) at the week of dropout.

and the serum level was 4.8 (3.7) µg/mL. There was a predictable and significant relationship between the topiramate dose administered and the serum concentration achieved (r=0.71; $P<.001$). There was, however, no significant correlation between serum topiramate level and the percentage of heavy drinking days among those who completed week 14 (r=0.04; P=.72). Different time sampling in obtaining the weekly serum topiramate levels might, however, have contributed to some variability in the results. No numerical difference existed between the topiramate and placebo groups in mean breath alcohol concentration; the average reading was 0.002%. Retention rates at study end among those randomized were 61.2% (112 of 183) for the topiramate group and 76.6% (144 of 188) for the placebo group ($P<.001$). The attrition rates due to adverse events were 18.6% (34 of 183) for the topiramate group and 4.3% (8 of 188) for the placebo group ($P<.001$).

Adverse events that were reported to occur in 10% or more of participants were paresthesia, headache, taste perversion, fatigue, anorexia, nausea, insomnia, difficulty with concentration and attention, nervousness, difficulty with memory, somnolence, diarrhea, sinusitis, dyspepsia, injury, dizziness, influenza-like symptoms, pruritus, and myalgia (TABLE 4); all except headache, nausea, sinusitis, dyspepsia, injury, influenza-like symptoms, and myalgia were more frequent for topiramate compared with placebo recipients. Four participants in each treatment group experienced a serious adverse event. In the topiramate group, one participant had myopia and another had cholelithiasis. Also, one participant had convulsions and loss of consciousness; however, these could not be attributed to the study medication. In contrast, in the placebo group, one participant died following a cardiac arrest associated with gastrointestinal tract bleeding and seizures. The precipitating incident could not be determined. Also, 3 separate individuals in the placebo group had a tibial plateau fracture, abnormally elevated serum liver enzymes, and diverticulitis.

Table 4. Adverse Events During Treatment Occurring in 10% or More of Participants[a]

	No. (%) of Participants With Adverse Events		
	Topiramate (n = 183)	Placebo (n = 188)	*P* Value[b]
Paresthesia	93 (50.8)	20 (10.6)	<.001
Headache	44 (24.0)	60 (31.9)	.09
Taste perversion	42 (23.0)	9 (4.8)	<.001
Fatigue	41 (22.4)	33 (17.6)	.24
Anorexia	36 (19.7)	13 (6.9)	<.001
Insomnia	35 (19.1)	30 (16.0)	.42
Difficulty with concentration/attention	27 (14.8)	6 (3.2)	<.001
Nervousness	26 (14.2)	14 (7.5)	.04
Difficulty with memory	23 (12.6)	13 (6.9)	.07
Somnolence	22 (12.0)	19 (10.1)	.56
Diarrhea	22 (12.0)	16 (8.5)	.27
Dizziness	21 (11.5)	10 (5.3)	.03
Pruritus	19 (10.4)	2 (1.1)	<.001
Nausea	19 (10.4)	31 (16.5)	.08
Dyspepsia	16 (8.7)	22 (11.7)	.35
Influenza-like symptoms	16 (8.7)	21 (11.2)	.44
Sinusitis	15 (8.2)	26 (13.8)	.08
Myalgia	14 (7.7)	19 (10.1)	.41
Injury	8 (4.4)	22 (11.7)	.01

[a] If a participant experienced more than 1 adverse event within a category, the participant is counted once under that category. Participants with more than 1 occurrence of an adverse event are summarized under the most related category. The World Health Organization Adverse Reactions Terminology dictionary modified for topiramate (version 1992, 3rd quarter) was used for coding.
[b] Calculated using the χ^2 test.

COMMENT

Topiramate was significantly more efficacious than placebo at reducing the percentage of heavy drinking days, improving all other self-reported drinking outcomes, and decreasing plasma GGT in a heterogeneous and geographically diverse population of alcohol-dependent individuals receiving weekly BBCET to promote medication adherence for 14 weeks.

The prespecified analytic method for this study, a repeated-measures mixed model, adjusts for missing data on the basis that it occurred at random. Even though we used the inverse-weighting method to show that the differential dropout rate, which was higher in the topiramate group, had little effect on outcome for the primary outcome variable (ie, percentage of heavy drinking days), we reported an even more conservative analysis of imputing all missing data with the baseline value as the primary analytic approach. This was done to determine what we think is the absolute lower bound of the treatment difference between topiramate and placebo. The consistency of topiramate's therapeutic effect was evidenced by the demonstration of clinical efficacy over placebo using these 3 separate inferential methods. We propose that topiramate's therapeutic effect that improves drinking outcomes is probably due to its diversity of pharmacological action.[1] Further research elucidating the combination of neuropharmacological processes associated with topiramate's therapeutic effect could, therefore, enhance development of more potent medicines.

Irrespective of statistical model, topiramate's therapeutic effect was evident no later than week 4, and this was maintained throughout the trial. It would, therefore, be of clinical interest to determine whether a smaller ceiling dose of topiramate than that tar-

geted in this study (ie, topiramate dose <300 mg/d) would be as efficacious over the length of the trial period. If so, this would enhance topiramate's utility because there was a trend toward an increased frequency of adverse events with dose. Furthermore, it also would be of interest to determine whether lengthier periods of topiramate treatment would be associated with sustained or more substantial reductions in heavy drinking.

Our findings provided validation that individuals with alcohol dependence, while drinking heavily, can be treated safely and reliably with topiramate[16] (ie, without establishing abstinence before initiating treatment).

Plausibly, individuals with certain subtypes of alcoholism might benefit the most from treatment with topiramate. While we did not observe a differential treatment response by age of problem drinking onset, other types of subtype classification that could include genetics or other biomarkers might have provided additional information.

Our study had 3 limitations. First, while the pattern of adverse events was similar to that found in our previous study,[3] the more rapid titration was associated with decreased study adherence with taking the medication. Previously, when topiramate was titrated over an additional 2 weeks (ie, over 8 weeks rather than 6 weeks), retention rates were similar between the topiramate and placebo groups. Clinical sites least familiar with topiramate experienced more difficulties with retention, whereas completion rates among some experienced groups approached 90% (data not shown). We advise clinicians to use the slower titration schedule and to provide participants with focused education on managing emergent adverse events to maximize adherence with taking the medication. Second, as with most clinical trials in the alcohol dependence field, enrolled participants have to meet criteria enabling the conduct of a safe study. Because this cohort is often relatively healthier and perhaps more homogeneous than the general population of all those seeking treatment for alcohol dependence, our ability to generalize without restriction from this trial to clinical practice is limited. Third, this study did not have a follow-up period, so we could not determine whether, how many, and at what interval participants would have relapsed following medication withdrawal. Nevertheless, with respect to how people fare, on average, following treatment for alcoholism in a clinical trial, a meta-analysis of recent studies has shown that, even after a single treatment event, most can show substantial reductions in drinking up to 1 year afterward.[17]

Our finding in this study that topiramate is a safe and consistently efficacious medication for treating alcohol dependence is scientifically and clinically important. Alcoholism ranks third and fifth on the US and global burdens of disease, respectively. Discovering pharmacological agents such as topiramate that improve drinking outcomes can make a major contribution to global health. Because topiramate pharmacotherapy can be paired with a brief intervention deliverable by nonspecialist health practitioners, a next step would be to examine its efficacy in community practice settings.

Author Contributions: Dr Johnson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Anton, Ciraulo, Kranzler, Mann, O'Malley, and Swift contributed equally as coauthors.
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Role of the Sponsor: The sponsor was involved in all stages from study design through interpretation of the results including critical review of the manuscript. Data were managed initially and analyzed by Ortho-McNeil Janssen Scientific Affairs LLC and PharmaNet Inc, a contract research organization, and were interpreted by the study authors with input from Ortho-McNeil Janssen Scientific Affairs LLC clinical and statistical staff. An independent statistical analysis was performed by Daniel O. Scharfstein, ScD (see below). The entirety of the first draft was prepared by Dr Johnson. The draft was reviewed by all of the authors, who discussed it as a group at a scheduled meeting of the Topiramate for Alcoholism Advisory Board (see below) in New York on February 2, 2007. Amendments pertained to style and presentation, and no changes were made by the sponsor to the results or their interpretation from the initial draft or the results as presented at that meeting.
Independent Statistical Analysis: Daniel O. Scharfstein, ScD, conducted an independent statistical analysis at the Johns Hopkins University Bloomberg School of Public Health. Dr Scharfstein had access to the entire raw data set, study protocol, and prespecified plan for data analysis. Dr Scharfstein confirmed the accuracy and validity of the data and results presented in this article. He received compensation from Ortho-McNeil Janssen Scientific Affairs LLC to perform this independent statistical evaluation.
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