Oral Topiramate Reduces the Consequences of Drinking and Improves the Quality of Life of Alcohol-Dependent Individuals

A Randomized Controlled Trial

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Background: Topiramate, a fructopyranose derivative, was superior to placebo at improving the drinking outcomes of alcohol-dependent individuals.

Objectives: To determine whether topiramate, compared with placebo, improves psychosocial functioning in alcohol-dependent individuals and to discover how this improvement is related to heavy drinking behavior.


Participants: One hundred fifty alcohol-dependent individuals, diagnosed using the DSM-IV.

Interventions: Seventy-five participants received topiramate (escalating dose of 25 mg/d to 300 mg/d), and 75 had placebo and weekly standardized medication compliance management.

Main Outcome Measures: Three elements of psychosocial functioning were measured: clinical ratings of overall well-being and alcohol-dependence severity, quality of life, and harmful drinking consequences. Overall well-being and dependence severity and quality of life were analyzed as binary responses with a generalized estimating equation approach; harmful drinking consequences were analyzed as a continuous response using a mixed-effects, repeated-measures model.

Results: Averaged over the course of double-blind treatment, topiramate, compared with placebo, improved the odds of overall well-being (odds ratio [OR] = 2.17; 95% confidence interval [CI], 1.16-2.60; \( P = .01 \)); reported abstinence and not seeking alcohol (OR = 2.63; 95% CI, 1.52-4.53; \( P = .001 \)); overall life satisfaction (OR = 2.28; 95% CI, 1.21-4.29; \( P = .01 \)); and reduced harmful drinking consequences (OR = –0.07; 95% CI, –0.12 to –0.02, \( P = .01 \)). There was a significant shift from higher to lower drinking quartiles on percentage of heavy drinking days, which was associated with improvements on all measures of psychosocial functioning.

Conclusions: As an adjunct to medication compliance enhancement treatment, topiramate (up to 300 mg/d) was superior to placebo at not only improving drinking outcomes but increasing overall well-being and quality of life and lessening dependence severity and its harmful consequences.

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Topiramate, a sulfamate-substituted fructopyranose derivative, is efficacious at both reducing craving and heavy drinking, and improving abstinence among alcohol-dependent individuals.\(^1\) Conceptually, topiramate’s efficacy might be due to its contemporaneous actions at 2 neuronal systems that, combined, reduce mesocorticolimbic dopamine activity, a crucial mechanism by which alcohol exerts its rewarding effects.\(^2\) Topiramate facilitates the inhibitory neurotransmitter \( \gamma \)-aminobutyric acid on a nonbenzodiazepine receptor,\(^3\) thus decreasing the extracellular release of dopamine in the midbrain.\(^4\) Additionally, topiramate might suppress mesocorticolimbic dopamine activity by antagonizing the excitatory effects of glutamate receptors of the \( \alpha \)-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate types on these dopamine neurons.\(^5-8\) Topiramate’s antiglutaminergic effects may be more pronounced in chronic alcoholics, compared with nonpathological drinkers, because they have enhanced binding sites of both AMPA and kainate receptors.\(^6\)

Despite these exciting neuropharmacological effects of topiramate on drinking behavior, an important question pertaining to its overall clinical effectiveness remains. Does topiramate’s efficacy at improving drinking outcomes result in an ap-

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preciable improvement in quality of life or a reduction in the harmful psychosocial consequences of alcohol? This question reflects the fact that the deleterious psychosocial consequences of pathological drinking on social, occupational, or recreational activities are a defining characteristic of alcohol dependence syndrome. Indeed, the persistence of these harmful consequences of pathological drinking is critical to the concept of alcoholism as a chronic disease. As pharmacotherapy is targeted at the narrow focus of reducing the “symptom” of drinking, formal psychotherapies are often coadministered to reduce the harmful psychosocial consequences of pathological drinking. Yet, it is unclear whether it is sufficient to reduce the harmful psychosocial consequences of alcohol dependence simply by producing a marked reduction in drinking. Furthermore, studies that have yoked formal psychotherapy with pharmacotherapy are unable to address this question properly because the treatment effects observed from the “dose” of psychotherapy are at least equivalent to, and may be larger than, those resulting from the “dose” of pharmacotherapy. The present study provides a unique opportunity to address the question of whether drinking reductions can, at least in the short term, bring about significant reductions in the harmful psychosocial consequences of drinking. In this case, the pharmacotherapy was not coupled with psychotherapy but rather with a compliance-enhancement intervention to increase observance with taking the medication.

In this study we examine whether pharmacotherapy with topiramate, compared with placebo, in alcohol-dependent individuals receiving a standardized medication compliance treatment, is associated with a reduction in the harmful psychosocial consequences of drinking and an improvement in quality of life. We also examine the relationship between changes in psychosocial function and heavy drinking.

METHODS

SUBJECTS

We enrolled 150 men and women who had been diagnosed with alcohol dependence according to the DSM-IV and who were current drinkers. Subjects were 21 to 65 years old, scored 8 or higher on the Alcohol Use Disorders Identification Test (an assessment of personal and social harm consequence to alcohol consumption), and drank 21 or more (women) and 35 or more (men) standard alcohol drinks per week during the 90 days prior to enrollment. One standard drink was defined as 0.35 L of beer, 0.15 L of wine, or 0.04 L of 80-proof liquor. Enrolled subjects had a negative urine toxicological screen for narcotics, amphetamines, cannabinoids, or sedative-hypnotics at enrollment. We excluded individuals with a current DSM-IV Axis 1 diagnosis other than alcohol or nicotine dependence, with clinically significant alcohol-withdrawal symptoms or physical abnormalities, or who were compelled to receive alcohol treatment. Subjects were also excluded if they had received alcohol treatment within 30 days of recruitment or were pregnant or lactating. Abstinence at study entry was not an enrollment criterion but a treatment goal.

We received ethical approval for this study from the institutional review board at The University of Texas Health Science Center at San Antonio. We recruited individuals who responded to a newspaper or radio advertisement seeking participants for an alcohol treatment study between December 29, 1998, and April 11, 2001.

GENERAL PROCEDURES

At week 0 (baseline), after providing written informed consent, we established that the subjects were physically healthy from their medical history, physical examination results, electrocardiogram, and hematological and biochemical test results. Women took a urine pregnancy test to confirm that they were not pregnant. We assessed the overall severity of alcohol dependence with measures of that component on the Clinical Global Impression Scale (CGI-S). The CGI-S is a 7-point scale that ranges from 1 (reportedly abstinence and not seeking alcohol or “not addicted”) to 7 (reportedly drinking more and constantly seeking alcohol or “extremely, severely addicted”). We measured the psychosocial impact of drinking on multiple domains of general lifestyle with the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). The Q-LES-Q is composed of 93 items, each containing responses on a 5-point scale that ranges from 1 (“not at all or never”) to 5 (“all the time”). Ninety-one of these items were grouped into 8 summary scales. Five of the 8 summary scales were scored for all subjects and included physical health/activities (13 items; maximum score=65); subjective feelings (14 items; maximum score=70); leisure time activities (6 items; maximum score=30); social relationships (11 items; maximum score=35); and general activities (14 items; maximum score=70). We scored the other 3 summary scales when applicable, and these included work (13 items; maximum score=65); household duties (10 items; maximum score=90); and school/coursework (10 items; maximum score=50). We measured satisfaction with medication and overall life satisfaction with individual item scales, each with a maximum score of 5. We measured the specific and direct harmful consequences of drinking using the Drinker Inventory of Consequences (DrInC). Each of the 50 DrInC items was assessed on a 3-point scale ranging from “never or once or a few times” to “daily or almost every day.” These 50 DrInC items were further subdivided into 6 subscales: physical consequences (8 items; maximum score=24); interpersonal consequences (8 items; maximum score=24); social responsibility consequences (7 items; maximum score=21); intrapersonal consequences (10 items; maximum score=30); impulse control consequences (12 items; maximum score=36); and control items (3 items; maximum score=13); as well as a total consequences scale (45 items; maximum score=135). The total consequences scale was the sum of all subscales other than the control items subscale. A lower score denoted a decreased adverse consequence of drinking as compared with a higher score. The control items subscale was the sum of 5 reverse-scored validity items. We also measured self-reported drinking, past 90 days, using the timeline follow-back method.

We enrolled eligible participants at the beginning of week 1. From week 1 through week 12, we assessed participants weekly on the CGI-S. On a second CGI item, Clinical Global Impression–Change (CGI-C) scale, we quantified the change in global functioning on a 7-point scale ranging from 1 (“very much improved”) to 7 (“very much worse”). We assessed participants every 3 weeks on the Q-LES-Q and the DrInC. We measured self-reported drinking using the timeline follow-back method, and performed weekly safety checks that included an assessment of vital signs (ie, blood pressure, pulse, and temperature), weight, and breath alcohol concentration each week. Additional health and safety checks, including electrocardiograms; adverse events; concomitant medications; withdrawal symptoms; hematological, biochemical, pregnancy, and drug tests; and physical examinations, were performed at scheduled intervals from week 1 through week 12.
MEDICATION: SUPPLY, DOSES, BLINDING, AND COMPLIANCE

Topiramate and matching placebo tablets were provided by Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ. From the beginning of week 1 through week 12, escalating doses of matching placebo or topiramate (up to 300 mg/d) were provided according to the schedule described previously as an adjunct to weekly brief behavioral compliance enhancement treatment (BB CET). The maximum topiramate dose was administered between week 8 and week 12. Subjects administered either topiramate or placebo received an identical number of tablets. Medication was dispensed in blister packs labeled with identification, study and visit numbers, and date. Medication packs returned at each weekly visit, along with the calendar-based, pill-taking schedule, were used to calculate the pill count.

BRIEF BEHAVIORAL COMPLIANCE ENHANCEMENT TREATMENT

A standard minimum psychosocial adherence enhancement procedure, BB CET emphasizes that medication compliance is critical to changing the alcoholic’s drinking behavior. Minimal interventions, such as the brief advice of Edwards et al., have proven to be effective and beneficial treatments for alcoholism. We modeled our BB CET 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. Trained nurse practitioners performed BB CET weekly for 12 weeks using a standardized manual. Nurses’ adherence to the protocol for delivering BB CET was monitored by the same physician (N.A.-D.) for the duration of the study.

OUTCOME MEASURES

Our 4 outcome measures of psychosocial functioning over the 12-week trial period were as follows: CGI-S, a Global Clinicians’ Rating of the severity of alcohol dependence (completed weekly); CGI-C, a Global Clinicians’ Rating of improvement in psychosocial functioning from baseline (completed weekly, except at week 0); Q-LES-Q, an overall measure of psychosocial functioning and quality of life (completed at weeks 0, 3, 6, 9, and 12); and DrInC, self-ratings of the specific and direct harmful consequences of drinking (completed at weeks 0, 3, 6, 9, and 12).

STATISTICAL ANALYSES

Data management was conducted according to the Food and Drug Administration guidelines of Good Clinical Practice. Data quality (including double-data entry) was supervised by a master’s-level database coordinator and statistician. Individual subject plots were checked for unusual values and completeness. Outcome measure values were validated as correct against the case records. Data were analyzed using Statistical Analysis System version 8.1 (SAS Institute Inc, Cary, NC).

We defined 2 binary responses based on the CGI-S and CGI-C scales. On the CGI-S, an individual without a clinically significant addiction was defined as scoring either 1 (reportedly abstinent and not seeking alcohol) or 2 (reportedly drinking less and occasionally seeking alcohol); individuals with higher scores were considered to have a clinically significant severity of alcohol dependence. Similarly, on the CGI-C scale an individual was defined as having a clinically significant improvement if he or she scored 1 (very much improved) or 2 (much improved); individuals with higher scores were considered not to have experienced a clinically significant improvement. Treatment effects were estimated as the odds ratio (OR) of topiramate vs placebo for these 2 longitudinal binary responses. Odds ratios measured the relative likelihood for achieving these responses between topiramate and placebo. The generalized estimating equation approach was used to account for the correlation of observations within individuals with autoregressive structure as the working correlation matrix, as implemented by SAS PROC GENMOD software. Analyses were adjusted for subject baseline characteristics including age, sex, age at onset, and drinks per day during the 90-day period prior to enrollment.

We categorized Q-LES-Q summary scales as low and high scores. This categorization was based on the different percentiles of the maximum possible scores, ranging from the 50th to the 90th percentiles. For a study week, if a subject had a score higher than the given percentile of the maximum score, he or she was designated to have a high score; otherwise, it was determined that the score was low. Pearlstein et al. suggested that a score of 70 or higher represents a “normal” quality of life. We observed that increasingly stringent cutoff points demonstrated the contrasts between the treatment groups more effectively (Figure 1), so we chose the 90th percentile of the maximum score as the final discrimination criterion to do hypothesis testing. “High” scores were considered to be indicative of improvement. We used the generalized estimating equation approach to do repeated-measures testing on the summary scales of physical health/activities, subjective feelings, leisure time activities, social relationships, general activities, work, household duties, satisfaction with medication, and overall life satisfaction and contentment. We used autoregressive within-subject correlation for determining robust estimates. Treatment effects were ORs comparing the likelihood of high vs low scores in the topiramate and placebo groups. We adjusted all models for the baseline summary score, age, and sex. Using the 90th percentile of the maximum possible summary score as the cutoff point, we tested whether the ORs comparing the topiramate vs placebo groups were equal to 1, with P values and 95% confidence intervals (CIs). We also estimated ORs and the corresponding P values and 95% CIs at the last visit using logistic regression. We used exact logistic regression for testing the OR of satisfaction with medication at the last visit, due to quasi-complete separation. We could not do hypothesis testing on the summary scale of school/coursework owing to the small sample size.

For the analysis of the DrInC subscales, we applied logarithmic transformations to the subscales plus 1 to enhance the normality of the residuals. We used general linear models and repeated-measures models with interaction of time and treatment group to model slopes that estimated the change in DrInC score per unit increase in the study period (ie, every 3 weeks) within the topiramate and placebo groups. We used SAS PROC MIXED software and adjusted for the intrasubject correlation by using a compound symmetry covariance structure based on the Akaike Information Criterion and the Schwarz Bayesian Criterion. We estimated robust parameters. We contrasted the slopes of change in the scores per unit increase in the study period between the topiramate and placebo groups. We also used analysis of covariance to estimate and contrast the means of the topiramate and placebo groups at the 12th week for each subscale. All models were adjusted for the baseline score, age, and sex.

Finally, we characterized the relationship between our psychosocial measures and drinking behavior for the topiramate group. Our purpose was to examine whether the topiramate-associated reductions in heavy drinking were associated with predictable improvements in clinical condition and quality of life, and a reduction in the harmful consequences of alcohol consumption. For the drinking component, we calculated the percentage of heavy drinking days (PHDD), defined as the days...
for which the number of drinks was 5 or greater for men and 4 or greater for women, divided by the number of study days. We then divided the PHDD metric into 4 fixed quartiles (0-25, 25-50, 50-75, and 75-100). For the CGI-S and CGI-C scales, we calculated the number of subjects in each drinking quartile who were categorized as “reportedly abstinent and not seeking alcohol” or “significantly improved,” respectively. For the Q-LES-Q scale, we calculated the number of subjects with “high” scores (ie, improvement) in each drinking quartile. Since the DrInC scale is a continuous variable, we displayed its trend across time alongside that of PHDD. Type I error was controlled by conducting only planned analyses.

RESULTS

In each group, 75 subjects received treatment (Figure 2). We have shown that at baseline the topiramate vs placebo groups had similar past-90-days baseline drinking levels (mean=9.59, SD=7.01 vs mean=8.85, SD=4.42 drinks/day); age (mean=41.51, SD=8.75 vs mean=42.05, SD=8.83 years); sex distribution (30.6% vs 26.6% were women); ethnic distribution (61.3% vs 66.6% were white); social class (34.6% vs 37.3% were from social class 1); severity of addiction; and age at onset of problem drinking (48% vs 44% were early-onset alcoholics).1 At study end, participants who received topiramate compared with those on placebo had significantly superior improvement on all drinking outcomes, including 27% fewer heavy drinking days (P<.001).1 These improvements in self-reported drinking were corroborated by the objective biochemical marker of transient alcohol consumption, plasma γ-glutamyl transferase.1 A mean of 83.0 (SD, 4.9) tablets were taken in the topiramate group, compared with 82.0 (SD, 4.3) in placebo group. The adverse events reported more frequently for topiramate compared with placebo recipients were dizziness (28.0% vs 10.7%; P=.01); paresthesia (57.3% vs 18.7%; P<.001); psychomotor slowing (26.7% vs 12.0%; P=.02); memory or concentration impairment (18.7% vs 5.3%; P=.01); and weight loss (54.7% vs 26.7%; P=.001). No serious adverse events occurred.1

The CGI-S and CGI-C scores decreased over time, and after we adjusted for subject characteristics at baseline, the estimated OR of topiramate vs placebo was 2.63 for being “reportedly abstinent and not seeking alcohol,” with 95% CI from 1.52 to 4.53 (P=.001), and 2.17 for being “significantly improved,” with 95% CI from 1.16 to 2.60 (P=.01).1

On the Q-LES-Q, the odds of obtaining “high” scores for the topiramate compared with the placebo group increased with rising percentiles of the maximum possible subscale score over the study period (Figure 1). Thus, increasingly strict criteria for improved quality of life were accompanied by a corresponding rise in the Q-LES-Q scores in the topiramate compared with the placebo group. For all Q-LES-Q summary scales, the estimated odds of “high” scores based on the 90th percentile cutoff point were higher in the topiramate compared with the placebo group, and achieved statistical significance on the subscales of physical health/activities (3.32; 95% CI, 1.48-7.46; P=.004); subjective feelings (3.57; 95% CI, 1.77-
Nevertheless, at study end, there was 1 subject in the topiramate group. Thus, we used exact logistic regression to test the null hypothesis. We were unable to model school/coursework data because of the reduced sample size, as only a few of our subjects were attending school or participating in ongoing academic activities (5 in the placebo group and 15 subjects had a “high” score (44.1%) in the topiramate group. Table 2 presents a reduction for both groups on all the DrInC subscales at study end, with topiramate-associated decreases being significantly greater than those for placebo.

For descriptive purposes, we explored the relationship between PHDD and CGI-C, overall life satisfaction on the Q-LES-Q, and total DrInC scales over the study period. Figure 3 shows that between baseline and study end there was a shift in the number of subjects from the higher quartiles of PHDD to the lowest quartile, and a corresponding increase in the number of individuals who were “significantly improved” in the lowest quartile. Similarly, Figure 4 shows a shift in the number of subjects from the higher quartiles of PHDD to the lowest, and a corresponding increase in the number of individuals who had “high” scores on the Q-LES-Q in the lowest PHDD quartile. Figure 5 is consistent with these findings, showing an almost parallel relationship between the reduction in the harmful consequences of drinking and the reported PHDD across the study period. On aggregate, Figures 3 to 5 show that there was a dramatic trend in the reduction of heavy drinking between baseline and study end for recipients of topiramate. Further, there was a predictable and apparently direct relationship between the reduction in PHDD and an improvement in the individuals’ clinical condition and quality of life, as well as a reduction in the harmful consequences of alcohol consumption.

**COMMENT**

Our results show that topiramate is more effective than placebo at improving the quality of life and overall clinical condition and at reducing the severity of addiction and harmful consequences of heavy drinking. Topiramate’s effect at improving psychosocial functioning was robust, with an increasing trend toward better outcomes as treatment progressed. Strikingly, these reductions in the harmful consequences of drinking displayed a similar trend to the reduction in the PHDD. Thus, as heavy drinking was reduced, more individuals experienced an improvement in psychosocial functioning. We did not do a formal correlational test between psycho-social functioning and heavy drinking as these variables are obviously colinear. Further, due to the colinearity of these variables, it is not possible for us to attribute any cause-and-effect prediction to the relationship between psychosocial improvements and reduced heavy drinking. It is tempting to speculate that the reductions in heavy drinking might explain a substantial part of this effect. This is because the principal target of the “minimum” behavioral intervention was to enhance compliance with medication rather than to target any antecedents, triggers, or perpetuating psychosocial factors associated with the heavy drinking. Nevertheless, the possibility that the “minimum” behavioral intervention promulgated some ongoing psychosocial improvement cannot be discounted entirely because such brief treatments have been shown previously to be effective treatment for alcoholism in a variety of settings. Also, we did not have an appropriate “control” group—that is, participants who received the “minimum” intervention alone (without adjunctive placebo medication); therefore, the independent effects of our “minimum” intervention cannot be teased out from the effects of the medication alone.

We propose that topiramate’s effectiveness at improving psychosocial functioning in alcohol-dependent individuals is not medication specific; such an effect could also be expected for other pharmacotherapies if they had similar efficacy. For instance, findings from a large open-label trial suggest that psychosocial improvements...
among alcoholics receiving acamprosate occur irrespective of the nature of psychosocial support. Topiramate has, however, not been compared directly with other putative therapeutic medications for treating alcoholism; its comparative efficacy is unknown. Nevertheless, based on the limited data from this single clinical trial, the effect size for topiramate’s treatment efficacy suggested that it is at least as efficacious as other promising medications such as naltrexone or acamprosate for treating alcoholism.29 If this is the case, the central issue with pharmacotherapy research might not be whether it is coupled with a “minimum” or “maximum” psychosocial intervention, but rather whether the combined treatment produces a substantial decrease in drinking. That is, the harm of the alcohol dependence syndrome can be lessened during treatment irrespective of the type of psychosocial intervention and pharmacotherapy, so long as it is effective at reducing heavy drinking. The important implication here is that even though abstinence is the “gold standard” of alcoholism treatment and was the goal of this study, a harm-reduction strategy based on reducing heavy drinking may be a worthwhile treatment goal, especially if the patient will not or cannot become abstinent. Indeed, a recent influential review of the literature has suggested that harm reduction strategies might be as beneficial as abstinence-oriented approaches, particularly if treatments are directed to accommodate the preferences and needs of the individual or target populations.30 The concern often raised with this harm-reduction approach is that alcoholics who drink even at “social” levels (1 and 2 drinks per day for women and men, respectively) might be at greater risk of relapse than abstinent individuals31 as they are being exposed continuously to the most powerful drinking cue of all, actual alcohol consumption.32,33 Therefore, when the medication is stopped, relapse to a pattern of heavy drinking...
will be quite likely. In gainsay, these arguments are based on the controversial premise of “controlled” drinking studies; the corresponding analogy here would be that as the delivery of pharmaco-therapy is relatively short, such as a few weeks or months, individuals who do not become abstinent by study end might be at an increased risk of relapse. The appropriateness of such an analogy to pharmacotherapy studies can be questioned in 2 ways. First, there is insufficient knowledge about the long-term outcomes of individuals who complete such studies with varying levels of drinking outcome, such as from abstinence to social drinking, by study end. Second, the more apt scenario might be to consider an individual who is drinking at social levels at the end of a pharmacotherapy study as being in “partial remission” but not “cured.” Thus, the pertinent question becomes whether this “partial remission” could be maintained or abstinence ultimately achieved if efficacious medication is prescribed long-term or indefinitely. That is, instead of short-term pharma-cotherapy, if it is accepted that alcoholism is a chronic disorder requiring continuous and possibly lifetime pharmaco-logical treatment, in the same manner as the provision of insulin to a diabetic is essential, could pharmaco-therapy not simply be provided as long-term treatment to maintain clinical improvement? Also, will the psychosocial gains in general lifestyle and well-being obtained by pharmacotherapy-driven, long-term maintenance of social drinking levels operate to provide time for the alcoholic to heal “naturally” and ultimately become abstinent as he or she becomes more able to be productive in society? Finally, what individual or group characteristics determine those subjects who might do just as well with medication-maintained social drinking compared with those who remain abstinent?30,34 Research is needed in this understudied area of alcoholic pharma-cotherapy to provide answers to these questions. Not only would this provide pharmacological knowledge on the long-term management of alcoholism, but it might help to bridge the gap between research and practice, where patients are often seen for prolonged periods and often over a lifetime.

One caveat of our study was that it was not designed to provide for post-treatment follow-up, so it is not known how long these psychosocial improvements were sustained. What can be said, however, is that even when a “minimum” compliance enhancement intervention is coupled with effective pharmacotherapy, there are important gains in psychosocial functioning during treatment. Our combined regimen of topiramate and BBCET not only treats the “symptom” of drinking but is effective at improving psychosocial functioning during treatment that encompasses the alcohol dependence syndrome. We note that the treatment effects described in this trial may only be possible with moderately dependent alcoholics, and may not generalize to those with the most severe and entrenched form of the disease.

In summary, our results continue to provide evidence that topiramate is a safe and effective treatment for alcohol dependence syndrome, and that pharmaco-
pies that reduce heavy drinking can significantly improve quality of life and reduce the consequences of alcohol consumption.

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