Oral topiramate for treatment of alcohol dependence: a randomised controlled trial

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Summary

Background Topiramate, a sulphamate fructopyranose derivative, might antagonise alcohol’s rewarding effects associated with abuse liability by inhibiting mesocorticolimbic dopamine release via the contemporaneous facilitation of γ-aminobutyric acid activity and inhibition of glutamate function. We aimed to see whether topiramate was more effective than placebo as a treatment for alcohol dependence.

Methods We did a double-blind randomised controlled 12-week clinical trial comparing oral topiramate and placebo for treatment of 150 individuals with alcohol dependence. Of these 150 individuals, 75 were assigned to receive topiramate (escalating dose of 25–300 mg per day) and 75 had placebo as an adjunct to weekly standardised medication compliance management. Primary efficacy variables were: self-reported drinking (drinks per day, drinks per drinking day, percentage of heavy drinking days, percentage of days abstinent) and plasma γ-glutamyl transferase, an objective index of alcohol consumption. The secondary efficacy variable was self-reported craving.

Findings At study end, participants on topiramate, compared with those on placebo, had 2·88 (95% CI –4·50 to –1·27) fewer drinks per day (p=0·0003), 26·2% more days abstinent (p=0·0003), and a log plasma γ-glutamyl transferase ratio of 0·07 (–0·11 to –0·02) less (p=0·0046). Topiramate-induced differences in craving were also significantly greater than placebo at reducing drinking, promoting abstinence, and decreasing craving in individuals who are dependent on alcohol.

Interpretation Topiramate (up to 300 mg per day) is more efficacious than placebo as an adjunct to standardised medication compliance management in treatment of alcohol dependence.

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See Commentary page 1666

Introduction

Dopamine pathways that originate in the ventral tegmental area and project to the nucleus accumbens and cortex are widely thought to mediate alcohol’s rewarding effects (including craving) associated with its abuse liability.1 Alcohol intake, by decreasing γ-aminobutyric acid receptor activity in the ventral tegmental area, disinhibits γ-aminobutyric acid-mediated tonic inhibition of ventral tegmental area dopamine neurons2 and facilitates dopamine neurotransmission.3 Glutamnergic pathways from the hippocampus and cortex modulate activity of γ-aminobutyric acid in the midbrain.4 Therefore, it is of interest that individuals with chronic alcoholism might have more glutamate binding sites in the brain than people who are not dependent on alcohol,5 including those of the α-aminooxy-5-methylisoxazole-4-propionic acid and kainate types in the hippocampus,6 an effect that could result in facilitated dopamine neurotransmission in the midbrain.7

Topiramate is a sulphamate fructopyranose derivative that: facilitates γ-aminobutyric acid function through a non-benzodiazepine site on the γ-aminobutyric acid-A receptor,7 thus decreasing extracellular release of dopamine in the midbrain;8 and antagonises glutamate activity at α-aminooxy-5-methylisoxazole-4-propionic acid and kainate receptors.9

We, therefore, postulated that topiramate would be an effective treatment for alcohol dependence because it had the potential to decrease mesocorticolimbic dopamine activity after alcohol intake and to antagonise chronic changes induced by alcohol at the α-aminooxy-5-methylisoxazole-4-propionic acid and kainate glutamate receptors.

As a proof-of-concept test of this hypothesis, we did a randomised, double-blind, 12-week controlled clinical trial to determine whether topiramate (escalating dose of 25 mg per day to 300 mg per day) would be more effective than placebo at reducing drinking, promoting abstinence, and decreasing craving in individuals who are dependent on alcohol.

Methods

Patients

We enrolled 150 men and women who had been diagnosed with alcohol dependence according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV).9 Participants were 21–65 years old; scored 8 or greater on the alcohol use disorders identification test,10 which assesses the personal and social harm after alcohol consumption; reported drinking on average at least 21 standard drinks per week for women and at least 35 per week for men, during the 90 days before enrolment; and had a negative urine toxicological screen for narcotics, amphetamines, or sedative hypnotics at enrolment. One standard drink is defined as 0·35 L of beer, 0·15 L of wine, or 0·04 L of 80 proof liquor.

ARTICLES
Although abstinence at study entry was not an enrolment criterion, we instructed participants to attempt drinking cessation and to participate in the medication compliance treatment. We excluded participants if they had: a current axis I psychiatric diagnosis other than alcohol or nicotine dependence; important alcohol withdrawal symptoms (clinical institute withdrawal assessment for alcohol-revised [25 mg tablets 100 mg and 25 mg tablets 100 mg tablet 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 25 mg tablets 100 mg and 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Adherence to brief behavioural compliance-enhancement treatment procedures was monitored once a week throughout the study by the same study physician. Brief behavioural compliance-enhancement treatment sessions usually lasted about 20 min. (Copies of the brief behavioural compliance-enhancement treatment manual can be obtained from BAJ.)

We used four primary efficacy variables to capture self-reported drinking behaviour from the start of week 1 to the end of week 12 using the timeline follow-back method: drinks per day (drinks consumed divided by number of study days); drinks per drinking day (average of the 12 weeks of drinks per drinking day ratio, in which every weekly drinks per drinking day ratio was the number of drinks consumed during the given study week divided by the number of drinking days for that week); percentage of heavy drinking days (days for which the number of heavy drinking days divided by the number of drinking days was five or greater for men and four or greater for women, divided by the number of study days); and percentage of days abstinent (the number of non-drinking days divided by the number of study days).

The fifth primary efficacy variable, an objective index of drinking—plasma γ-glutamyl transferase concentration—was calculated as the average of the log plasma γ-glutamyl transferase for each of weeks 3, 6, 9, and 12 divided by the log plasma γ-glutamyl transferase at week 0, all subtracted from 1. The sixth, a secondary efficacy variable, was self-reported craving from the start of week 1 to the end of week 12, which was measured on the 14-item obsessive compulsive drinking scale. This variable was comprised of four factors derived empirically by principal component structure analysis:20 drinking obsessions—obsessional thoughts related to drinking; automaticity of drinking—five items that assessed the extent to which drinking was controlled or uncontrolled; interference due to drinking—three items that assessed the extent to which drinking interfered with work and social functioning, and the degree to which being prevented from drinking was distressing; and alcohol consumption—two items that assessed the quantity and frequency of alcohol consumption. We did not include the alcohol-consumption factor in the efficacy analyses since this measure is co-linear with self-reported drinking, which was assessed by the timeline follow-back method.

Statistical analysis

Power calculations were based on the need to select an ample cell size to detect significant treatment differences between topiramate and placebo as an average of the 12-week drinking outcomes in an analysis of covariance model. Effect sizes were derived from a previous clinical trial in which ondansetron (4 μg/kg twice daily) was more effective than placebo at reducing mean drinks per day (3-13 [95% CI 2.01–4.25] vs 1.56 [0.71–2.41], respectively) in people whose alcohol dependence was of early onset.21 Assuming an α of 0.05, we calculated that 75 participants in each group would provide 95% power to detect a difference of similar magnitude between topiramate and placebo.

We managed the data according to US Food and Drug Administration guidelines of good clinical practice. Data quality (including double-data entry) was supervised by a masters-level database coordinator and statistician. Individual plots were checked for unusual values and completeness. Efficacy values were validated as correct against case records. Data were analysed with SAS version 8.1.

Treatment compliance measures were study attendance rate and medication compliance (pill count). Physical health and safety measures were: breath alcohol concentration at clinic attendance; clinical institute withdrawal assessment for alcohol-revised; vital signs; haematological, biochemical, and urine drug screens; use of concomitant medication; attendance at psychosocial treatments outside the study; and adverse-event profile.

Data were analysed by intention to treat. Data were randomised, with an urn randomisation procedure, to treatment at the beginning of week 1 by JDR. All participants, those administering the interventions, and those assessing the outcomes were unaware of the group assignment. Participants were assigned randomly to one of two groups (ie, escalating doses of topiramate or placebo) after balancing based on sex, average drinks per day, and age of onset. Participants received their randomised, double-blind study medication at the beginning of week 1. The first recorded response to double-blind medication could, therefore, not be measured until the end of week 1. Evaluable participants were, therefore, those who returned to the clinic for assessment at the end of week 1. Hence, treatment response was measured from the end of week 1 until the end of week 12.

We considered the outcome measures before and at baseline as candidate covariates to control for prestudy and study enrolment effects, respectively. However, the final analytical model included only the outcome measures at week 0 as covariates because they were significantly related to outcome and adjusted for group differences at study enrolment. Analysis of double-blind treatment response, which was adjusted for study enrolment effects, was investigated from the end of week 1 until the end of week 12. An interaction term was included in the final model for drinks per drinking day because there was a significant interaction between this measure’s covariate at study entrance and treatment. Additionally, covariates were plotted against the residuals to determine their random normal distribution. In all cases, these plots showed significant covariates to be linear and resulted in valid analyses.

As a data-reduction technique, self-reported drinking and craving response were calculated as the mean of weeks 1 to 12. These average response analyses preserved sample size since all participants with at least one outcome measure (ie, end of week 1) were included in the efficacy analysis. Since these means have a variance inversely proportional to the number of visits attended,22 the outcome analysis was weighted by the number of study weeks completed with non-missing data. The residuals of this two-way analysis of covariance, weighted for missing data effects, were checked for normality by calculating their skewness, kurtosis, and homogeneity of variance by histograms and against the predicted outcome.

Two secondary analyses of the drinking data were used to characterise the time and magnitude for achieving a clinically important treatment response. First, we calculated the probability of the time to the first day of achieving 14 continuous days of abstinence or non-heavy drinking for the topiramate and placebo groups with the Kaplan-Meier method. Second, Cox’s proportional hazards model was used to estimate the relative probability (ie, magnitude of the treatment response) between topiramate and placebo for achieving continuous periods of abstinence or non-heavy drinking from 7 to 28 days. For the Cox’s regression model, investigation of potential confounding variables yielded only chronological age, sex, and drinks per day at week 0 as covariates for inclusion in the final model.

Secondary analysis of the craving data included use of Pearson’s correlation coefficients to determine the strength of the association between mean scores on the three...
The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report.

Results

75 participants in each group received treatment (figure 1). Table 2 shows the participants’ baseline characteristics. Self-reported and objective drinking measures were lower at the study end (end of week 12) than at the start of the study (end of week 1) in both groups (p<0·0001 for all comparisons).

Over the course of treatment, topiramate was significantly more effective than placebo at improving drinking outcomes on drinks per day, drinks per drinking day, percentage of heavy drinking days, percentage of days with at least one drinking day, and percentage of drinks per day. No significant differences were found between groups for days abstinent, days of heavy drinking, or percentage of drinking days.

Table 3: Mean difference between topiramate and placebo averaged over trial period

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Difference (95% CI)</th>
<th>p</th>
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<tr>
<td>Self-reported drinking</td>
<td></td>
<td></td>
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<tr>
<td>Drinks per day</td>
<td>–1·06 (–1·17 to –0·35)</td>
<td>0·0037</td>
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<tr>
<td>Drinks per drinking day</td>
<td>–1·20 (–1·37 to –0·34)</td>
<td>0·0049</td>
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<tr>
<td>Heavy drinking days (%)</td>
<td>–14·80 (–22·58 to –7·02)</td>
<td>0·0002</td>
</tr>
<tr>
<td>Days abstinent (%)</td>
<td>11·62 (9·69 to 19·27)</td>
<td>0·0031</td>
</tr>
<tr>
<td>Log plasma γ-glutamyl transferase ratio</td>
<td>–0·036 (–0·065 to –0·008)</td>
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</tr>
<tr>
<td>Obsessive compulsive drinking scale factor scores</td>
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<td></td>
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<td>Drinking obsessions</td>
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<tr>
<td>Automaticity of drinking</td>
<td>–1·53 (–2·38 to –0·68)</td>
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<td>Interference due to drinking</td>
<td>–0·77 (–1·28 to –0·26)</td>
<td>0·0034</td>
</tr>
</tbody>
</table>

Table 2: Baseline demographic and psychopathological characteristics of participants

<table>
<thead>
<tr>
<th>Group assignments</th>
<th>Topiramate (n=75)</th>
<th>Placebo (n=75)</th>
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<tr>
<td>Age of alcoholism onset</td>
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<tr>
<td>Early</td>
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<td>33</td>
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<tr>
<td>Late</td>
<td>39</td>
<td>42</td>
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<td>Demographic variables</td>
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<tr>
<td>Age (years)</td>
<td>41·51 (8·75)</td>
<td>42·05 (8·83)</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Women</td>
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<td>20</td>
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<td>Ethnic origin</td>
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<tr>
<td>White</td>
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<td>2</td>
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<tr>
<td>Hispanic</td>
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<td>23</td>
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<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Social class*</td>
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</tr>
<tr>
<td>1–3</td>
<td>26</td>
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<td>4–6</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>7–9</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77·44 (13·60)</td>
<td>81·11 (13·77)</td>
</tr>
</tbody>
</table>

Counts and proportions for categorical items were compared among groups with the χ² test for independence either at one time or accumulated over several timepoints. Secondary analyses included assessment for the time to the emergence of significant treatment differences between topiramate and placebo, for group differences at study end, and for an interaction between treatment condition and age of problem-drinking onset. Only planned analyses as defined in the protocol were done.

Objective drinking marker, plasma γ-glutamyl transferase, using a similar statistical strategy to the self-reported measures except that week 0 was used as the baseline, and response was calculated over the four assessment periods (ie, weeks 3, 6, 9, and 12) as an average log ratio of the week 0 value. Plasma γ-glutamyl transferase ratios were log transformed for the residuals of the general linear model to meet the requirement of normality.

Counts and proportions for categorical items were compared among groups with the χ² test for independence either at one time or accumulated over several timepoints. Secondary analyses included assessment for the time to the emergence of significant treatment differences between topiramate and placebo, for group differences at study end, and for an interaction between treatment condition and age of problem-drinking onset. Only planned analyses as defined in the protocol were done.
abstinent, and log plasma γ-glutamyl transferase ratio (table 3). The interaction term between the week 0 drinks per drinking day and treatment group in the final model for drinks per drinking day was significant (p=0.0026).

Significant differences between topiramate and placebo on the self-reported and the objective drinking measures started at weeks 6 and 8, respectively (figures 2 and 3; table 4). The probability of not abstaining decreased with time in the treatment group, and was significantly lower than in the placebo group (figure 4). The maximum relative probability (ie, magnitude of the treatment response) between topiramate and placebo for achieving continuous abstinence or non-heavy drinking was 8.86 at 24 days and 5.13 at 18 days, respectively (figure 5).

As an average of subscale scores on the obsessive compulsive drinking scale during the study, patients on topiramate had significantly reduced drinking obsessions, automaticity of drinking, and interference due to drinking (table 3). As in the drinking data, the anticraving effects associated with topiramate compared with placebo were greater at the end of the trial than when averaged across the study (figure 6; table 4). Correlations between the mean obsessive compulsive drinking scale factors 1–3 and timeline follow-back self-reported drinking data were, respectively: drinks per day r=0.52 (p<0.0001) and r=0.28 (p=0.014); drinks per drinking day r=0.53 (p<0.0001) and 0.29 (p=0.012); percentage of heavy drinking days r=0.54 (p<0.0001) and 0.29 (p=0.012); and percentage of days abstinent r=0.33 (p=0.003) and −0.17 (p=0.148).

The treatment response to topiramate compared with placebo did not differ between patients with early-onset and late-onset alcoholism for any of the six primary outcome measures (all p>0.05).

Our results showed a significant effect on six response variables related to actual drinking measures. The probability of making a type 1 error, on any one to all six variables, ranges from 0.047 to less than 0.0001. A factor analysis for all six response variables indicates three dimensions: obsessive compulsive drinking scale, plasma γ-glutamyl transferase, and the drinking dimension that includes the four drinking measures (drinks per day, drinks per drinking day, percentage of heavy drinking days, and percentage of days abstinent). The type 1 error rate is less than 0.0022 for any two independent comparisons, and is less than 0.0001 for any three independent comparisons. For the drinking data, even when the 90-day timeline follow-back measures associated

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**Figure 2:** Change in self-reported drinking outcomes from baseline (week 0) by study week

Values are mean (95% CI). Numbers of participants are those with available data at each time.
with outcome were used in the model, rather than just the week 0 measures, the results were similar.

A mean of 83·0 (SD 4·9) tablets were taken in the topiramate group, compared with 82·0 (4·3) in the placebo group. Of the participants who completed the study, 46 of 55 on topiramate and 44 of 48 on placebo tolerated the maximum dose (300 mg per day for topiramate or six tablets for placebo; p=0·221). 55 people in the topiramate group completed the study compared with 48 in the placebo group (p=0·218), and the mean length of time stayed in the study did not differ between groups (10·1 weeks [SD 0·8] vs 9·2 weeks [0·9], p=0·177).

We recorded no serious adverse events. The following adverse events were reported more frequently in the topiramate group than in the placebo group: dizziness (28·0% vs 10·7%, p=0·007); paraesthesia (57·3% vs 18·7%, p<0·0001); psychomotor slowing (18·7% vs 5·3%, p=0·012); and weight loss (54·7% vs 26·7%, p=0·001). The average weight change was greater in the topiramate group than in the placebo group (–1·40 kg [0·39] vs +0·61 kg [0·53], respectively, p=0·002). Other than those noted above, cumulative adverse events did not differ between the two groups within the central nervous system (17·3% vs 18·7%, p=0·832); gastrointestinal (40·0% vs 34·7%, p=0·500); cardiovascular (1·3% vs 1·3%, p=1·000); urinary/psychosexual (4·0% vs 2·7%, p=0·649); and ear, nose, and throat or upper respiratory (41·3% vs 36·0%, p=0·502). Attrition from adverse events was 4% (three of 75) and 7% (five of 75) for the topiramate and placebo groups, respectively.

Positive breath-alcohol concentrations (values above 0) occurred on only 5·34% of all participant visits, with no difference between the topiramate and placebo groups. Furthermore, an alcohol concentration above 0·08% was recorded in three patients in the topiramate group and in one in the placebo group (p=0·311). Alcohol withdrawal symptom scores did not differ significantly between the groups (mean clinical institute withdrawal assessment for alcohol-revised 0·77 [SD 0·23] for topiramate vs 0·90 [0·20] for placebo, p=0·400). Testing positive for one or more of the nine agents in the urine drug screen was much the same in the topiramate (nine patients) and placebo (ten)
groups (p=0.806). The number of participants using drugs in the topiramate and placebo groups were, respectively: marijuana (six vs five); cocaine (three in each group); opiates (one in each group); phencyclidine (one in each group); and amphetamines (one vs none).

Rates of any concomitant medication use and of psychosocial attendance outside the study were similar for the topiramate (41 and three, respectively) and placebo (51 and five) groups.

**Discussion**

Our results show that topiramate is more effective than placebo at reducing drinking and promoting abstinence in alcohol-dependent individuals who are seeking treatment. Topiramate’s treatment effect on drinking outcome was robust, with increasing differences compared with the placebo as the study progressed. Furthermore, topiramate-induced improvement in self-reported drinking outcomes was corroborated by corresponding decreases in the objective measure, plasma γ-glutamyl transferase.

Topiramate’s effectiveness on the self-reported drinking measures started at about the 200 mg per day dose (ie, week 6). Topiramate dose was, however, increased over time up to week 8, and the independent effects of time and topiramate dose cannot therefore be segregated. Topiramate doses lower than 200 mg per day might be effective if delivered throughout the study period. Results of studies27 with topiramate for seizure-treatment have shown a linear dose-response profile. Hence, there is a foundation for future studies to characterise better topiramate’s dose response in treating alcoholism.

Although what constitutes craving is controversial, most would accept that it is a multidimensional construct that attempts to capture the propensity or compulsion to act on ideas, impulses, or innate drives to use an abused substance such as alcohol.20 Therefore, reducing craving should improve the drinking outcomes of people with alcohol dependence who are seeking treatment. Thus, that topiramate effectively reduced craving on all three obsessive-compulsive drinking scale factors is important. Craving reductions were also significantly correlated with the reduction in self-reported drinking. We postulate, although we did not measure it directly, that topiramate combats craving by inhibiting alcohol-induced release of dopamine in the midbrain. The monophasic decrease in
alcohol craving across the obsessive-compulsive drinking scale subscales could also be the consequence rather than a cause of reduced drinking or abstinence.

Typically, adverse events were of mild intensity. Slightly more participants on topiramate completed the study compared with those on placebo. The clinically small difference in weight loss among those receiving topiramate was probably due to their lower baseline intake from alcohol. Women were more likely than men to report adverse events (data not shown), presumably because of their lower body weight. Overall, topiramate’s adverse-event profile was similar to that reported for other indications, and we think it is safe for use in treating alcohol addiction.

Abstinence was not a requirement for study entry. It was, however, the treatment goal. We reinforced this target by advising participants at study entry to attempt abstinence. One advantage of enrolling into clinical studies people addicted to alcohol who are currently drinking is that treatment is delivered proximate to when help is sought. This strategy could be of particular practical importance to devising an effective treatment approach in primary-care settings, where such people with alcohol dependence usually present during a drinking crisis.

Similar to previous findings, the largest drinking reduction during the study was seen between the screening and enrolment periods. We have attributed this effect to the fact that the participants had to keep track of how much they were drinking, they had better control of their consumption. This effect does, however, underscore the need to enrol alcohol-dependent individuals with drinking histories into clinical trials.

Topiramate’s effectiveness did not vary significantly by age of onset—a variable used to segregate early-onset alcoholics with high familial disease loading and antisocial behaviours from those with more psychosocially determined, or late-onset, alcoholism. Early-onset alcoholism can be mediated mainly by serotonergic and possibly opioid function. For example, the effectiveness of ondansetron (a serotonin-3 antagonist) is manifest only in those with early-onset alcoholism, and response to naltrexone (a μ opiate antagonist) is greatest in those with a family history of alcoholism in first-degree relatives.

Topiramate would, therefore, not be expected to have a differential effect on this alcoholic subtype, since no pharmacological effects have been shown at either of these receptors. Thus, the effectiveness of topiramate might be mediated through neurochemical processes such as the central function of γ-amino-butyric acid, which might influence drinking behaviour in individuals with early-onset and late-onset alcoholism. In view of the scientific interest in combining putative therapeutic agents to increase the effectiveness of treatment for alcoholism, topiramate’s properties could make it an attractive candidate for co-treatment with other specific medications for treating either early-onset or late-onset alcoholism.

Typically, medications are developed from animal studies, through human beings, with eventual clinical testing. However, few promising drugs for treatment of alcohol dependence have been developed through this approach. Studies in animals have provided the theoretical framework for understanding alcohol’s rewarding effects, but which animal models best approximate human drinking behaviour is not known. To our knowledge, there have been no previous studies directly examining topiramate’s effects on drinking behaviour in either animals or human beings. We propose that bolder approaches should at least be considered where the scientific rationale is compelling and the putative therapeutic medication is known to be safe and preferably approved for human use by the US Food and Drug Administration. Some serendipity was associated with our clinical discovery; however, use of a dose-escalating regimen gave us greater chances of seeing an effect.

Finally, our results provide evidence that topiramate is a safe and effective medication for treatment of alcoholism. Topiramate’s development for treatment of alcoholism should garner scientific interest, since few effective medications are available for this indication. We continue to advance treatment of alcoholism with further proof-of-concept studies from animals to human beings, and vice versa, across a range of behavioural-pharmacological paradigms.

**Contributors**
B A Johnson thought of the neuroscientific basis and study rationale for the research. B A Johnson, N Ait-Daoud, J D Roache, C C DiClemente, and M A Javars designed the protocol, did the research, and wrote and edited the report. C Bowden participated in the analysis and interpretation of the data and in the writing and editing of the report. N Ait-Daoud also was involved with study implementation and quality control. C C DiClemente, B A Johnson, and N Ait-Daoud developed the psychological intervention. K Lawson and J Z Ma developed the statistical procedures, did the statistical analyses, and assisted with interpretation of the results.

**Conflict of interest statement**
None declared.

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