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-amino-butyric 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=0·0006), 3·10 (–4·88 to –1·31) fewer drinks per drinking day (p=0·0009), 27·6% fewer heavy drinking days (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 those of placebo, of similar magnitude to the self-reported drinking changes, and highly correlated with them.

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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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-amino-butyric acid receptor activity in the ventral tegmental area, disinhibits γ-amino-butyric acid-mediated tonic inhibition of ventral tegmental area dopamine neurons[2] and facilitates dopamine neurotransmission.[2] Glutaminergic pathways from the hippocampus and cortex modulate activity of γ-amino-butyric acid in the midbrain.[3] 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,[3] including those of the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate types in the hippocampus,[4] an effect that could result in facilitated dopamine neurotransmission in the midbrain.

Topiramate is a sulphamate fructopyranose derivative that: facilitates γ-amino-butyric acid function through a non-benzodiazepine site on the γ-amino-butyric acid-A receptor,[5] thus decreasing extracellular release of dopamine in the midbrain;[6] and antagonises glutamate activity at α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate receptors.[7]

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-amino-3-hydroxy-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).[8] Participants were 21–65 years old; scored 8 or greater on the alcohol use disorders identification test,[9] 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.

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 1 psychiatric diagnosis other than alcohol or nicotine dependence; important alcohol withdrawal symptoms (clinical institute withdrawal assessment for alcohol-revised[10] score >15); clinically significant physical abnormalities (ie, on physical examination, electrocardiogram recording, haematological assessment, biochemistry including a bilirubin concentration, and urinalysis); history of or current renal impairment, renal stones, seizures, or unstable hypertension; were pregnant or lactating; taking medications with a potential effect on alcohol consumption or a carbonic anhydrase inhibitor; being compelled to receive treatment for alcohol dependence to avoid imprisonment or loss of employment; or were receiving treatment for alcohol dependence within 30 days before enrolment.

Ethics approval was provided by the institutional review board at The University of Texas Health Science Center at San Antonio. Participants were recruited between December 29, 1998, and April 11, 2001, by newspaper or radio advertisements.

Procedures

At baseline (week 0), after providing written informed consent, we assessed participants on: physical health—medical history and physical examination, vital signs (ie, blood pressure, pulse, and temperature), 12-lead electrocardiogram, haematological and biochemical laboratory studies, including a urine drug test; breath alcohol concentration; urine pregnancy test; and psychiatric diagnosis—structured clinical interview for DSM IV;[11] age of problem-drinking onset—item B 28 of the comprehensive drinking profile;[12] severity of addiction—addiction severity index;[13] self-reported drinking—past 90 days, measured with the timeline follow-back method,[14] a widely used objective index of alcohol consumption; plasma γ-glutamyl transferase concentration[15] (Labcorps, Burlington, NC, USA); craving—obsessive compulsive drinking scale;[16] the clinical institute withdrawal assessment for alcohol-revised,[10] and concomitant medication.

We enrolled eligible participants at the beginning of week 1, after a review of the haematological, biochemical, and urine tests. We also assessed participants on: vital signs; weight; breath alcohol concentration; timeline follow-back; obsessive compulsive drinking scale; clinical institute withdrawal assessment for alcohol-revised; adverse events; concomitant medication use, and psychosocial treatment attendance outside the study. From the beginning of week 1 to the end of week 12, we dispensed double-blind tablets (ie, topiramate up to 300 mg per day or placebo) according to the schedule in table 1 as an adjunct to brief behavioural compliance-enhancement treatment once a week.

From weeks 2 to 12, we assessed participants once a week for vital signs, breath alcohol concentration, timeline follow-back, obsessive compulsive drinking scale, clinical institute withdrawal assessment for alcohol-revised, adverse-event profile (gathered systematically by trained practitioners using a modified version of the systematic assessment for treatment emergent events questionnaire,[17] concomitant medications, an enhanced pill-count technique with a calendar-based prompting system, and the frequency of psychosocial treatment attendance outside the study. At weeks 3, 6, 9, and 12, we repeated the plasma γ-glutamyl transferase measurements. Urine pregnancy tests were reassessed at weeks 2, 4, 6, 8, 10, and 12. Haematological and biochemical variables and urine drug screens were reassessed at weeks 6 and 12. Physical examination was repeated at weeks 3, 7, and 11, with an electrocardiogram at week 12. Study weeks were interspersed by a maximum of 11 days (from Monday of the previous week to Friday of the current week).

Topiramate and matching placebo tablets were provided by Ortho-McNeil Pharmaceutical (Raritan, NJ, USA). Using a double-blind procedure, the study medications were administered by the escalation schedule in table 1 for the first 8 weeks (ie, up to topiramate 300 mg per day or placebo) and were then stabilised at that dose for weeks 8–12. Participants in each group received an identical number of tablets. We dispensed the study medications in blister packs labelled with identification, study and visit numbers, and date. The returned packs at each weekly visit, along with the calendar-based pill-taking schedule, were used to calculate the pill count.

Brief behavioural treatment to enhance compliance is a standard minimum psychosocial adherence enhancement procedure, which emphasises that medication compliance is crucial to changing the drinking behaviour of people who are dependent on alcohol. Minimal interventions, such as the brief advice of Edwards and colleagues,[18] are effective and beneficial treatments for alcohol dependence. Brief behavioural compliance-enhancement treatment also has a practical advantage in that it can be delivered by nurses or general practitioners in a primary-care setting while they are dispensing and monitoring the medication. The brief behavioural compliance-enhancement treatment was modelled on the clinical management condition in the US National Institute of Mental Health collaborative depression trial, which was used as an adjunct to the medication condition.[19] For this study, brief behavioural compliance-enhancement treatment was done by trained nurse practitioners who used a standardised manual.

Week	Morning dose	Afternoon dose	Total daily dose
1	0 mg	1×25 mg tablet	25 mg
2	0 mg	2×25 mg tablets	50 mg
3	1×25 mg tablet	2×25 mg tablets	75 mg
4	2×25 mg tablets	2×25 mg tablets	100 mg
5	2×25 mg tablets	1×100 mg tablet	150 mg
6	1×100 mg tablet	1×100 mg tablet	200 mg
7	1×100 mg tablet	1×100 mg and 2×25 mg tablets	250 mg
8	1×100 mg and 2×25 mg tablets	1×100 mg and 2×25 mg tablets	300 mg
9	1×100 mg and 2×25 mg tablets	1×100 mg and 2×25 mg tablets	300 mg
10	1×100 mg and 2×25 mg tablets	1×100 mg and 2×25 mg tablets	300 mg
11	1×100 mg and 2×25 mg tablets	1×100 mg and 2×25 mg tablets	300 mg
12	1×100 mg and 2×25 mg tablets	1×100 mg and 2×25 mg tablets	300 mg

Schedule is similar to that provided in the *Physicians' Desk Reference* (2000). The placebo and topiramate groups received the same number of tablets; placebo tablets were inactive.

Table 1: **Topiramate dose-escalation schedule**

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 drinks 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,[22] 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,[23] 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,[24] 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

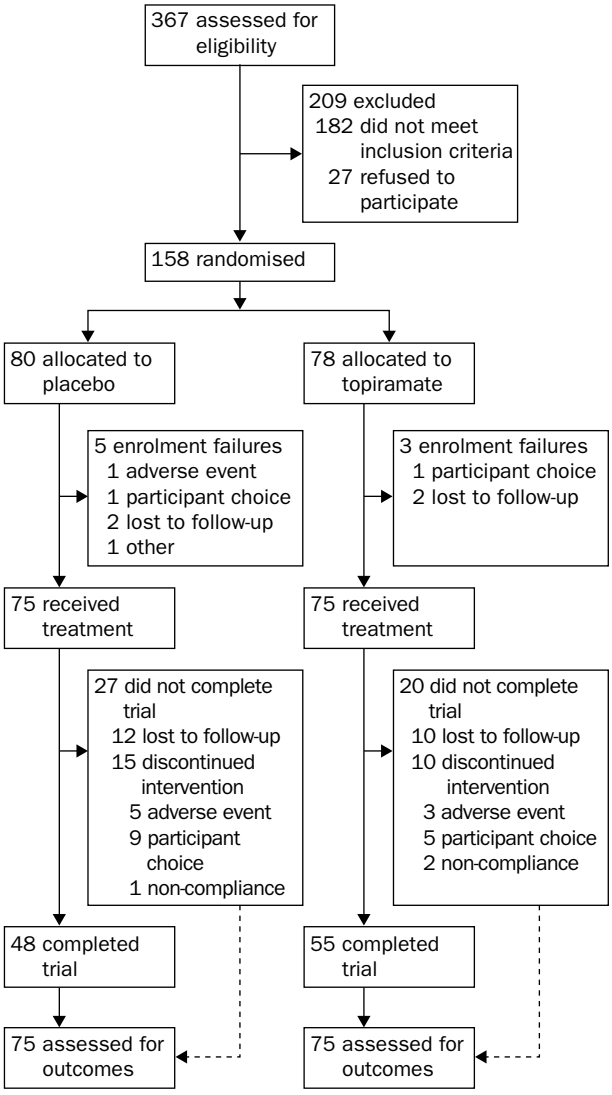


Figure 1: **Trial profile**

Trial completers were participants who completed all 12 weeks of double-blind treatment. Non-compliant individuals were those who did not complete the rating scales or questionnaires. Enrolment failures were those who received medication at the beginning of week 1 but did not return to the clinic for further assessment.

obsessive compulsive drinking scale factors (drinking obsessions, automaticity of drinking, and interference due to drinking) for each treatment group and self-reported drinking with the timeline follow-back method.[14]

We assessed the 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 χ^2 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.

	Topiramate (n=75)	Placebo (n=75)
Group assignments		
Age of alcoholism onset		
Early	36	33
Late	39	42
Demographic variables		
Age (years)	41·51 (8·75)	42·05 (8·83)
Sex		
Men	52	55
Women	23	20
Ethnic origin		
White	46	50
Black	2	2
Hispanic	25	23
Other	2	0
Social class*		
1–3	26	28
4–6	45	44
7–9	4	3
Weight (kg)	77·44 (13·60)	81·11 (13·77)
Measures of alcohol drinking		
Years since first report of problems with alcohol use	12·69 (9·09)	14·73 (9·87)
Drinks per day at intake (past 90 days)	9·59 (7·01)	8·85 (4·42)
Breath alcohol concentration	0·0048 (0·02)	0·0033 (0·01)
γ-glutamyl transferase (U/L)	73·28 (62·27)	70·48 (51·10)
Addiction severity index composite scores		
Medical	0·10 (0·26)	0·08 (0·17)
Employment	0·17 (0·17)	0·22 (0·26)
Alcohol	0·60 (0·17)	0·57 (0·17)
Drug	0·01 (0·00)	0·01 (0·00)
Legal	0·02 (0·09)	0·01 (0·09)
Family/social	0·47 (0·26)	0·42 (0·26)
Psychiatric	0·20 (0·17)	0·13 (0·17)
Clinical institute withdrawal assessment for alcohol-revised	1·64 (3·29)	1·82 (2·42)

Values are number of participants or mean (SD). *Defined by Hollingshead and Redlich.[25]

Table 2: **Baseline demographic and psychopathological characteristics of participants**

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report.

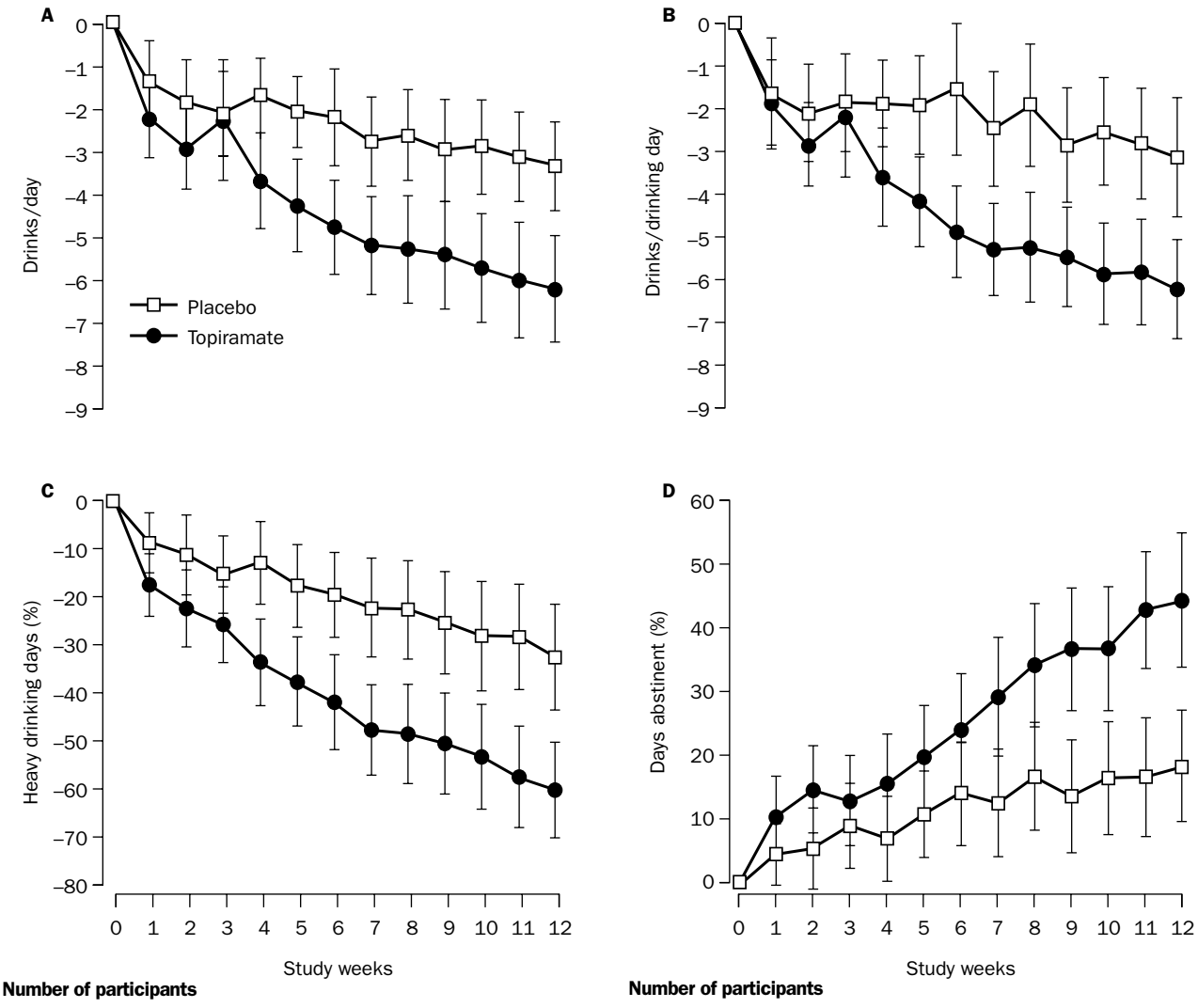
Results

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

	Difference (95% CI)	p
Outcome		
Self-reported drinking		
Drinks per day	–1·06 (–1·77 to –0·35)	0·0037
Drinks per drinking day	–1·20 (–2·02 to –0·37)	0·0049
Heavy drinking days (%)	–14·90 (–22·58 to –7·22)	0·0002
Days abstinent (%)	11·62 (3·98 to 19·27)	0·0031
Log plasma γ-glutamyl transferase ratio	–0·036 (–0·065 to –0·008)	0·0112
Obsessive compulsive drinking scale factor scores		
Drinking obsessions	–1·00 (–1·70 to –0·29)	0·0057
Automaticity of drinking	–1·53 (–2·38 to –0·68)	0·0005
Interference due to drinking	–0·77 (–1·28 to –0·26)	0·0034

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



Number of participants

	0	1	2	3	4	5	6	7	8	9	10	11	12
Topiramate	75	75	71	69	65	65	65	62	59	58	56	55	55
Placebo	75	75	71	69	62	60	54	52	52	48	49	49	48

Number of participants

	0	1	2	3	4	5	6	7	8	9	10	11	12
Topiramate	75	75	71	69	65	65	65	62	59	58	56	55	55
Placebo	75	75	71	69	62	60	54	52	52	48	49	49	48

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.

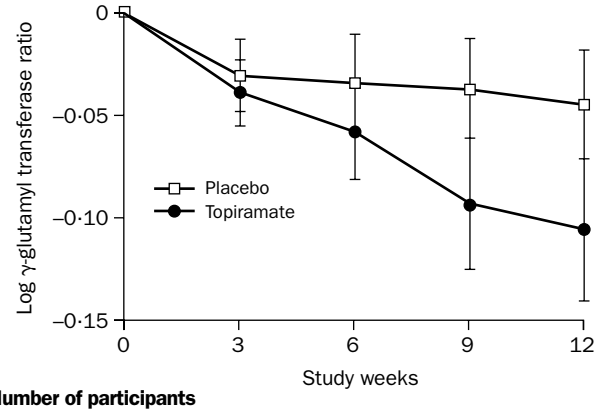
abstinent, and log plasma γ-glutamyl transferase ratio (table 3). The interaction term between the week 0 drinks per drinking day and treatment group in the final model for drinks per drinking day was significant (p=0·0026).

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



Number of participants					
Topiramate	71	70	65	56	54
Placebo	70	67	57	49	47

Figure 3: **Change from baseline (week 0) in log plasma γ-glutamyl transferase ratio at weeks 3, 6, 9, and 12**
Values are mean (95% CI). Numbers of participants reflect those with available data at each time.

with outcome were used in the model,[23] rather than just the week 0 measures,[26] 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 (26·7% *vs* 12·0%, p=0·023); memory or concentration impairment (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.

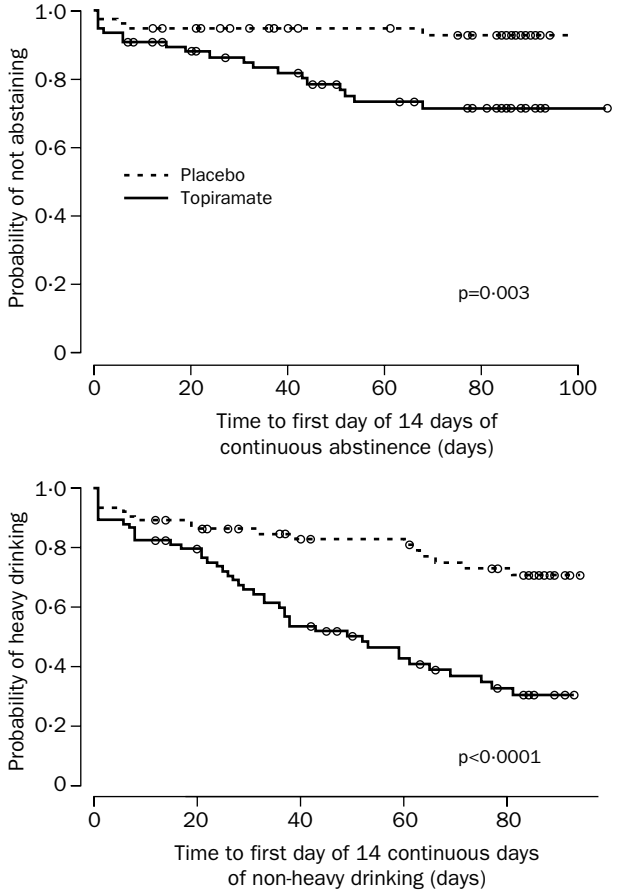


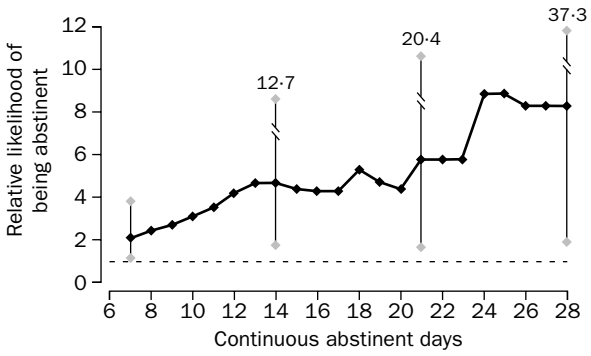
Figure 4: **Probability of non-abstinence (top) or heavy drinking (bottom) by time to achieving first of 14 days of continuous abstinence or non-heavy drinking**
Heavy drinking is defined as five or more drinks per day for men or four or more drinks per day for women.

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)

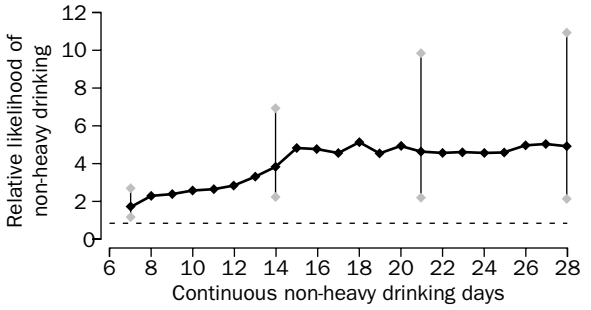
	Baseline*		Study end*		Difference (95% CI)†	p
	Topiramate (n=75)	Placebo (n=75)	Topiramate (n=55)	Placebo (n=48)		
Outcome						
Self-reported drinking						
Drinks per day	7·78 (5·12)	6·52 (4·38)	–6·24 (4·51)	–3·36 (3·58)	–2·88 (–4·50 to –1·27)	0·0006
Drinks per drinking day	9·71 (4·83)	8·58 (4·82)	–6·24 (4·26)	–3·14 (4·83)	–3·10 (–4·88 to –1·31)	0·0009
Heavy drinking days (%)	68·34 (31·62)	60·84 (32·17)	–60·34 (36·24)	–32·73 (37·98)	–27·61 (–42·20 to –13·02)	0·0003
Days abstinent (%)	21·73 (28·58)	25·99 (28·64)	44·21 (38·82)	18·00 (30·11)	26·21 (12·43 to 39·98)	0·0003
Log plasma γ-glutamyl transferase ratio‡	0	0	–0·106	–0·041	–0·07 (–0·11 to –0·02)	0·0046
Obsessive compulsive drinking scale factor scores						
Drinking obsessions	6·20 (3·00)	5·69 (2·96)	–3·35 (3·19)	–1·37 (3·02)	–1·98 (–3·28 to –0·69)	0·0031
Automaticity of drinking	9·31 (3·44)	8·73 (2·86)	–5·73 (3·95)	–3·12 (3·33)	–2·61 (–4·14 to –1·08)	0·0010
Interference due to drinking	4·97 (2·22)	4·40 (2·20)	–3·33 (2·37)	–1·61 (1·94)	–1·73 (–2·64 to –0·82)	0·0003

*Values are mean (SD). †Difference between topiramate and placebo at study end. ‡Objective drinking marker.

Table 4: **Outcomes at baseline and study end**



Continuous abstinent days	7	14	21	28
Number of abstinent participants				
Topiramate	29	19	14	13
Placebo	17	5	3	2



Continuous non-heavy drinking days	7	14	21	28
Number of non-heavy drinking participants				
Topiramate	52	44	30	28
Placebo	42	18	9	8

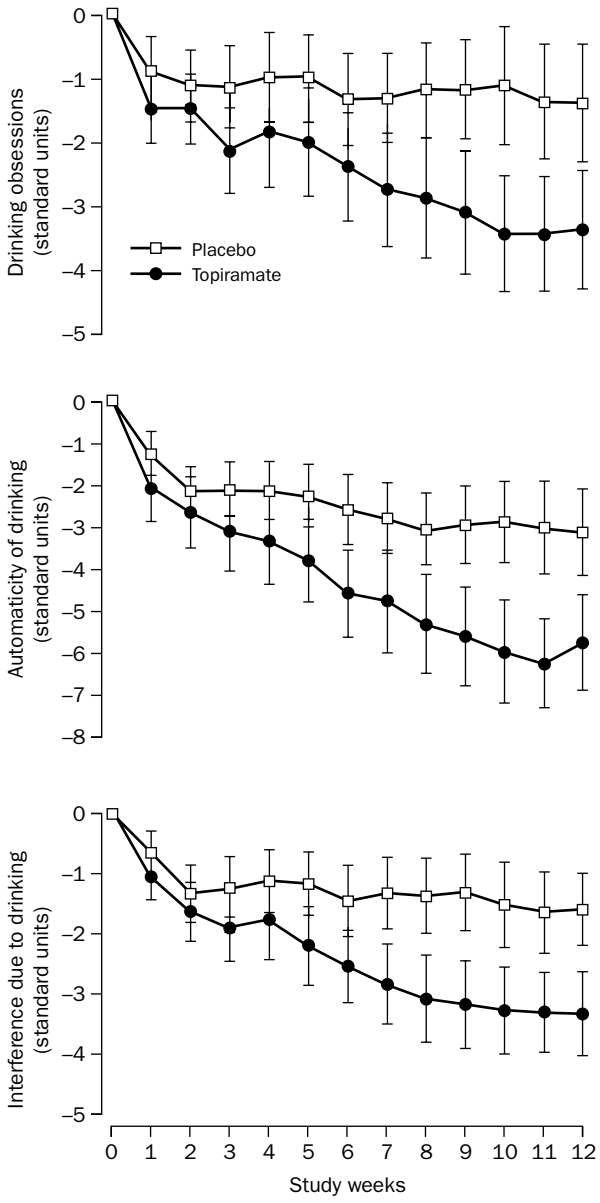
Figure 5: **Relative likelihood of achieving continuous abstinence or non-heavy drinking from 7 to 28 days**
Heavy drinking is defined as five or more drinks per day for men or four or more drinks per day for women. Bars are 95% CIs.

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 studies[27] with topiramate for seizure-



Topiramate	75	74	67	66	63	61	62	59	56	56	53	52	48
Placebo	75	72	71	68	59	57	52	51	50	47	45	46	43

Figure 6: **Change from baseline (week 0) in obsessive compulsive drinking scale factors by study week**
Values are mean (SE).

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 caloric intake from alcohol. Women were more likely than men to report adverse events (data not shown), presumably because of their lower bodyweight. 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,[21] the largest drinking reduction during the study was seen between the screening and enrolment periods. We have attributed this effect to the fact that because 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.[21] 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.[28] 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.[7] 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[28] 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 Javors 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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