

Comparing topiramate with naltrexone in the treatment of alcohol dependence*

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ABSTRACT

Aim To compare the efficacy of topiramate with naltrexone in the treatment of alcohol dependence. **Design** The investigation was a double-blind, placebo-controlled, 12-week study carried out at the University of São Paulo, Brazil. **Sample** A total of 155 patients, 18–60 years of age, with an International Classification of Diseases (ICD-10) diagnosis of alcohol dependence. **Methods** After a 1-week detoxification period, patients were assigned randomly to receive topiramate (induction to 300 mg/day), naltrexone (50 mg/day) or placebo. **Measurements** Time to first relapse (consumption of >60 g ethyl alcohol), cumulative abstinence duration and weeks of heavy drinking. **Findings** In intention-to-treat analyses, topiramate was statistically superior to placebo on a number of measures including time to first relapse (7.8 versus 5.0 weeks), cumulative abstinence duration (8.2 versus 5.6 weeks), weeks of heavy drinking (3.4 versus 5.9) and percentage of subjects abstinent at 4 weeks (67.3 versus 42.6) and 8 weeks (61.5 versus 31.5), but not 12 weeks (46.2 versus 27.8). Results remained significant after controlling for Alcoholics Anonymous attendance, which was higher in topiramate than in other groups. There were no significant differences between naltrexone versus placebo or naltrexone versus topiramate groups, but naltrexone showed trends toward inferior outcomes when compared to topiramate. **Conclusions** The results of this study support the efficacy of topiramate in the relapse prevention of alcoholism. Suggestive evidence was also obtained for superiority of topiramate versus naltrexone, but this needs to be verified in future research with larger sample sizes.

Keywords Alcoholics anonymous groups, alcohol dependence, pharmacotherapy, topiramate, naltrexone.

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INTRODUCTION

Alcoholism is a chronic medical disorder that ranks high as a cause of disability burden in most regions of the world. In Brazil, approximately 11% of the adult population can be considered alcohol dependent [1]. In spite of its psychological and social implications, alcohol dependence embodies many characteristics of other chronic medical diseases, including frequent relapses and the necessity for prolonged follow-up. The treatment of alcoholism, which has focused traditionally on psychosocial interventions, has also recently incorporated pharmacological components [2].

While pharmacotherapeutic interventions have been used commonly to treat alcohol withdrawal symptoms, there are few drugs to manage alcohol abuse and dependence on a long-term basis. Many different neurotransmitters seem to be affected by alcohol consumption, including opioid peptides, glutamate, serotonin, acetylcholine, adenosine, dopamine, noradrenaline and others [3]. As a result, medication development for alcohol treatment has been focused on a variety of medications with diverse mechanisms of action.

To date, three drugs have been approved for this indication by the Food and Drug Administration: disulfiram, naltrexone and acamprosate [4]. Several other

medications are under active study and are sometimes prescribed for alcoholism treatment on an unapproved or off-label basis. These include topiramate, ondansetron and some antidepressants [5,6]. Among these non-approved drugs, topiramate has emerged as the most promising medication for the treatment of alcohol dependence.

Topiramate is an anticonvulsant that facilitates the inhibitory action of the neurotransmitter gamma-aminobutyric acid (GABA) at its non-benzodiazepine receptor and reduces the excitatory action on glutamate receptors of the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate types [7,8]. Its action is similar to the approved medication, acamprosate, in that they are both thought to act on the glutamate system, but details of their mechanisms of action differ [9,10]. Topiramate has been shown in several clinical trials to improve outcomes for alcoholism treatment in comparison to placebo [11–15].

Naltrexone influences response to alcohol through modulation of the opioid system. Naltrexone has been examined for its ability to impact relapse to drinking by blocking the rewarding effects of alcohol [16,17]. Both acamprosate and naltrexone have been shown to be efficacious in the treatment of alcoholism, although their profile of activity differs with regard to supporting prolonged abstinence versus reducing the chances of relapse following the first drink [18,19]. The profile of topiramate's clinical effects has not been characterized in previous studies demonstrating efficacy.

In addition to identifying medications with new mechanisms of action, there is also a need to establish the comparative efficacy of various medications for the treatment of alcoholism. Although studies directly comparing naltrexone with acamprosate have been carried out [20–23], no randomized, double-blind study has evaluated the efficacy of topiramate versus other approved medications for the treatment of alcoholism. One study by Florez *et al.* [24] compared topiramate with naltrexone in a randomized but open-label trial. That study demonstrated a trend for superior outcomes with topiramate on some but not all measures of drinking. The present study provides a controlled comparison of the two medications using more sophisticated double-blind clinical trials methodology.

METHODS

Design

A randomized, double-blind, placebo-controlled clinical trial, with three parallel groups, was performed to determine the efficacy of topiramate and naltrexone in reducing drinking, promoting abstinence and decreasing

cravings in alcohol-dependent individuals. The treatment lasted 12 weeks. The study was conducted at the Clinical Hospital of the University of São Paulo, Brazil.

Participants

Male patients, 18–60 years of age, with an International Classification of Diseases (ICD-10; World Health Organization, 1992) [25] diagnosis of alcohol dependence who enrolled as out-patients in the Assistance Sector of the Interdisciplinary Group of Studies on Alcohol and Drugs at the University of São Paulo (GREA) were assessed for trial. This service (GREA) is dedicated exclusively to the treatment of males with alcohol and/or any other kind of drug abuse or dependence. All diagnoses were made by experienced psychiatrists who did not participate in this study.

Exclusion criteria were: (i) less than 18 years or more than 65 years of age; (ii) a current diagnosis of dependence or abuse of other substances except nicotine; (iii) patients with serious clinical coexisting diseases (e.g. inadequately controlled diabetes, cardiac failure, alcoholic cirrhosis); (iv) previous treatment with naltrexone or topiramate within 6 months of randomization; (v) concomitant psychiatric disorders that might require specific drug treatment; (vi) inability to give full informed consent; and (vii) clinical history of mental retardation, as it reduced the accuracy of the information given.

All subjects provided written informed consent and the study was approved by the Ethics Committee of the Clinical Hospital of the University of São Paulo, Brazil.

Measures

In the first interview, after a full history and clinical examination, patients who fulfilled entry criteria were evaluated with the Short Alcohol Dependence Data (SADD) [26], the Hamilton Depression Rating Scale (Ham-D) [27] and the Obsessive-Compulsive Drinking Scale (OCDS) [28]. The patients were also assessed on the two latter scales at the end of this research. Side effects were verified by the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale during the 12 weeks of the treatment [29]. In this research we employed a questionnaire on socio-demographic characteristics and alcohol and drug consumption history which is used commonly in the therapeutic setting of the Interdisciplinary Group of Studies on Alcohol and Drugs of the Clinical Hospital of the University of São Paulo, Brazil.

Procedure

Patients were informed about the study objectives and the nature of the treatment offered, which would consist of administration of one medication—topiramate,

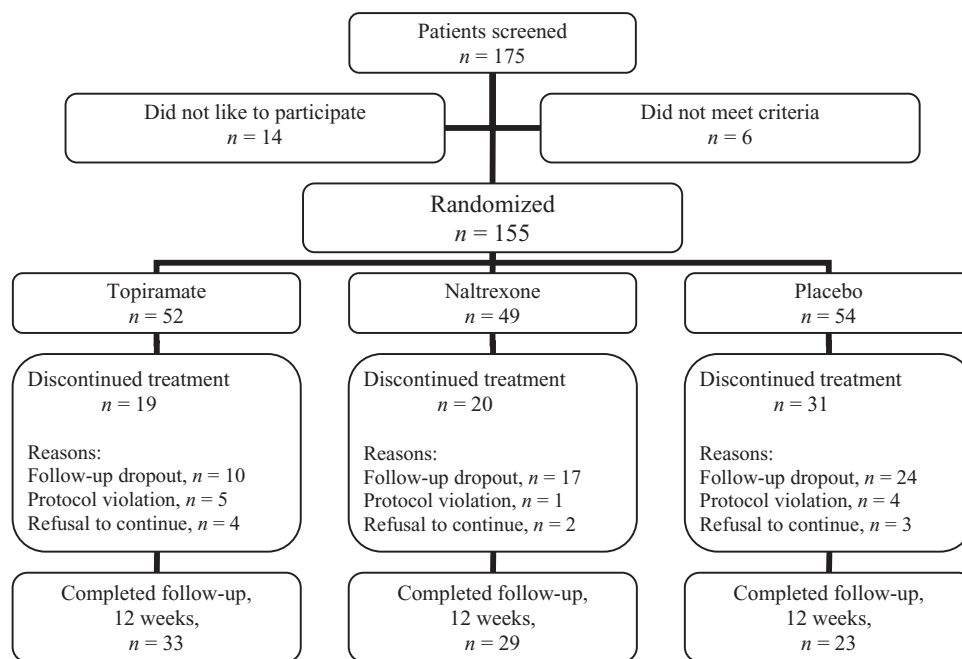


Figure 1 Consort flow chart, randomization and retention study

naltrexone or placebo, along with relapse prevention counselling and encouragement to participate in Alcoholics Anonymous (AA) groups. The side effect profiles of naltrexone and topiramate were described and subjects were told that the medication they received would be chosen at random. Subjects were also assured that they would not be withdrawn from the programme if they relapsed or failed to comply with the medication and that they could choose to leave the programme at any time.

Patients suffering from a severe relapse during the study could be admitted to a hospital for another alcohol withdrawal treatment while continuing their medication. In such cases patients were not considered as protocol violators, provided that they had remained on their medication and that the duration of the alcohol withdrawal treatment in hospital was fewer than 14 days.

Between 2005 and 2007, 175 patients entered treatment. Fourteen refused to take part in this study and six were excluded because of coexisting diseases, leaving a sample of 155. All screened patients were encouraged to participate in AA groups, but this was not an obligatory condition of taking part in this study (Fig. 1).

All patients received a 1-week detoxification prior to the initiation of double-blind treatment. This period was conducted on an out-patient basis and patients who manifested withdrawal symptoms were given medications such as lorazepam, up to 6 mg/day, and B₁ vitamin, 300 mg/day. Laboratory examinations, including liver function, were also collected during this period. The patients included in this study manifested from minimal to moderate withdrawal symptoms, which allowed them to be treated on an out-patient basis.

Following the 1-week detoxification period, the patients were assigned randomly to one of the three medication conditions through a random number list. Once a week, they received an envelope with two packages of seven capsules. One package was designated for morning dosing and the other for night-time; patients were instructed to take two capsules per day.

One group (n = 52) received escalating doses of topiramate, starting with 25 mg/day during week 1 and increasing to 300 mg/day by week 8. From week 8 to the end of week 12, this group received 300 mg/day of topiramate. Titration was achieved by schedule increments in the number of topiramate tablets or an equivalent number of matching placebo tablets inside capsules (Table 1). The second group (n = 49) received one placebo capsule and one capsule with naltrexone (50 mg) every day during 12 weeks, and the third group (n = 54) received two placebo capsules during 12 weeks. The naltrexone group took one placebo capsule in the morning and one capsule with naltrexone at night. All capsules in each treatment group had identical appearance and size and were manufactured by the pharmacy sector at the Psychiatric Institute of the Clinical Hospital of the University of São Paulo, Brazil. The size of the capsules was big enough to contain all tablets of topiramate; therefore, all capsules were identical for all three groups. This study has not been sponsored by any pharmaceutical industry.

The patients were assessed eight times during the trial at weeks 1, 2, 3, 4, 6, 8, 10 and 12 after the baseline assessment. Major variables recorded at each visit included clinical examination results, patients' self-reported quantity, frequency of alcohol consumption and

Table 1 Topiramate dose-escalating schedule.

Weeks	Morning capsule contents (g)	Night capsule contents (g)	Total dose
1	0 mg (placebo tablet)	1 tablet of 25 mg	25 mg
2	0 mg (placebo tablet)	2 tablets of 25 mg	50 mg
3	1 tablet of 25 mg	2 tablets of 25 mg	75 mg
4	2 tablets of 25 mg	2 tablets of 25 mg	100 mg
5	2 tablets of 25 mg	1 tablet of 100 mg	150 mg
6	1 tablet of 100 mg	1 tablet of 100 mg	200 mg
7	1 tablet of 100 mg	1 tablet of 100 mg and 2 tablets of 25 mg	250 mg
8–13	1 tablet of 100 mg and 2 tablets of 25 mg	1 tablet of 100 mg and 2 tablets of 25 mg	300 mg

drug side effects. For all participants, abstinence from alcohol was evaluated on the basis of the patient's self-report and by interviewing a family member, by measuring alcohol abuse hepatic indices—gamma glutamyl-transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and mean cellular volume (MCV)—at the start and at the end of this research.

At each appointment, medication compliance was evaluated by asking patients the following questions: (i) have you already forgotten to take your medications; (ii) are you sometimes neglectful in regard to your medicine time; (iii) do you skip your medicine time when you are feeling well; and (iv) when you feel bad due to the medicine, do you skip it? [30]. Only patients who answered affirmatively to all four questions were considered adherent to this study. Also, the capsules in the returned packages were counted (capsules taken subtracted from capsules given) at every appointment. Familial members, when available, were also interviewed for obtaining this information. All patients who were considered adherent to this study had taken all capsules adequately, according to medical recommendations. If patients refused to continue the use of these medications or stopped their usage, they would be discontinued from the research.

At each appointment, all patients received standardized brief cognitive behavioural interventions from their doctors who were blind to medication conditions. The overall goal of these interventions was to increase the person's ability to cope with high-risk situations that could precipitate relapses. At each visit, the drinking behaviour of the patients was reviewed and the medication compliance and motivation for change were improved using motivational interviewing strategies [31]. The patients were asked to monitor good and bad daily situations during all treatment and this was discussed with their doctors and, when possible, related to the drinking behaviour. The following topics were standardized and applied to each patient during this treatment: management of negative mood, assertiveness, drink refusal skills, enhancement of social support networks and relapse prevention.

Medications codes were revealed to researchers only after all patients had completed the study. Medication was dispensed under double-blind conditions. Only two pharmacists from the pharmacy sector at the Psychiatric Institute of the Clinical Hospital of the University of São Paulo knew which medication corresponded to the specific code. The packages containing the capsules were distributed to patients by two blinded research assistants, who also assessed patient outcomes throughout the study.

Outcome criteria

The main criterion for efficacy was drinking behaviour. For males, after a period of abstinence, the consumption of more than 40 g alcohol is regarded generally as a 'lapse', while the time to first 'relapse' would be drinking more than 60 or 90 g alcohol [32]. In our study, relapse was defined as the consumption of more than 60 g ethanol and heavy alcohol consumption was defined as the use of more than 90 g alcohol. The main outcome criteria were as follows.

- 1 Time to first relapse: defined as the period (in weeks) from the start of the treatment to the first alcohol consumption (more than 60 g ethanol).
- 2 Cumulative abstinence duration (CAD): defined as the total number of weeks of complete abstinence, calculated by adding all the periods of abstinence. If the patient reported having consumed alcohol at any day or sequence of days, the entire week (in which these days had been included) was considered a relapse period.
- 3 Weeks where there was heavy consumption of ethanol.
- 4 Subjective reports of side effects.

Patients who did not attend follow-up and whose outcome was unknown were considered to have dropped out of the trial.

Alcohol consumption during the treatment was determined using a daily monitoring card and compliance was evaluated by self-report, capsules count of the returned medication package and the daily monitoring card. Valid-

ity of the double-blind procedure was verified by obtaining a prediction from each patient and staff member as to whether a given individual had received active or placebo medication during the study.

Statistical analysis

Baseline differences among the three groups were determined using analysis of variance (ANOVA) for continuous variables and the χ^2 test for categorical variables. *Post-hoc* comparisons of each group were performed if there were statistically significant differences among these three groups. Certain continuous variables, such as the number of cigarettes smoked per day and monthly income, were not distributed normally according to Levene's criteria, so median changes from baseline were compared among the three groups using the Kruskal–Wallis non-parametric test, by which the test statistic H is calculated.

As all subjects were tested for depression measured by the Ham-D [27] and for craving on alcohol evaluated by the OCDS [28] at the start and at the end of this study, we combined these two dependent variables assessed at study end and adjusted them for differences in three covariates, which were baseline total scores on the Ham-D, the OCDS and the SADD. Statistical analysis was performed using multivariate analysis of covariance (MANCOVA) to determine whether the composite Ham-D, OCDS varied as a function of medication condition after controlling for the three baseline psychometric measures. Hepatic function indices (GGT, AST, ALT, MCV) were also assessed at the start and at the end of this study. These were combined into a single hepatic function measure and analysed with hepatic function scores obtained at the start of this study as covariates. The aim of this analysis was to verify if the means of these dependent variables differ as a function of different types of medication used, after adjustment for covariates. Both procedures involving MANCOVA were possible due to the homogeneity of variance–covariance matrices and normality of sampling distributions, according to Levene's criteria.

Statistical analysis of the main efficacy criteria followed the intention-to-treat (ITT) principle, which considers any randomized patient who took at least one dose of the trial medication as appropriate for the evaluation. Patients who missed a visit or withdrew from the study were deemed to be non-abstinent at the time of missed visits. The primary outcome measure—time from study start to the first drink with more than 60 g ethanol—was analysed by Kaplan–Meier survival analysis, censoring missing data (log-rank test).

The Cox proportional hazards regression analysis was used to adjust for participation in AA, which was a potential confound for treatment outcomes. This method

models event (time to first relapse) rates as a log-linear function of predictors or covariates.

For all statistical tests performed, differences among the three groups were accepted as significant if they achieved the 0.05 level with two-tailed tests. Data were analysed using SPSS 14, Stata 9 and power analysis and sample size (PASS). We based our sample size on a previous study that compared two active medications (acamprosate and naltrexone) versus placebo in the treatment of alcohol dependence [20]. After conclusion of the study, we calculated the power of our sample size to detect differences among the means obtained for time to the first relapse versus the alternative of equal values, using an F -test with a 0.05 significance level.

RESULTS

Sample characteristics

As shown in Table 2, there were no significant differences among the groups at baseline on any socio-demographic, drug use, hepatic function or psychometric variables measured. Overall, the mean age of the sample was 44.3 [standard deviation (SD) = 8.4] years, 51.6% were married and 71% were white. The average quantity of alcohol used per day was 301 g (SD = 174) and mean score on the SADD was 29 (SD = 8.5); these values reveal that this sample was of moderate to severe alcohol dependence.

Treatment retention

Overall, 70 patients dropped out of the trial. Reasons for dropout were classified as refusal (13%), protocol violation (14%) or lost to follow-up (73%). Dropout rates were 57.4% among participants randomized to placebo, 40.8% among those randomized to naltrexone and 36.4% among those randomized to topiramate. Differences between conditions in overall dropout rates approached significance ($\chi^2_{(2)} = 5.10$, $P < 0.07$) and were statistically significant within the lost-to-follow-up category ($\chi^2_{(2)} = 7.73$, $P < 0.02$) with a significant difference between topiramate and placebo in *post-hoc* analysis.

Main efficacy results (ITT)

As shown in Table 3, the proportion of subjects who remained completely abstinent until the fourth week was statistically different among the groups ($\chi^2_{(2)} = 6.55$, $P = 0.04$). After Yates's correction, the topiramate group showed a higher proportion of abstinent subjects than the placebo group (Yates's correction = 6.53, 1 df, $P = 0.01$), with no significant differences between the naltrexone and placebo (Yates's correction = 0.75, 1 df, $P = 0.39$), or between the topiramate and naltrexone

Table 2 Baseline characteristics.

Characteristic	Placebo (n = 54)	Naltrexone (n = 49)	Topiramate (n = 52)
Age, mean (SD)	43.4 (8.8)	44.1 (7.2)	45.5 (9.2)
Marital status (%)			
Married	51.9	49.0	53.9
Single	11.1	20.4	19.2
Separated/widowed	37.0	30.6	26.9
Race (%)			
White	70.4	69.4	73.1
Black	3.7	4.1	13.5
Mixed race	25.9	26.5	13.5
Education (%)			
6th grade or less	20.4	26.5	26.9
7th–12th grade	27.8	28.6	26.9
High school graduate	38.9	34.7	32.7
Unfinished/complete college	13.0	10.2	13.5
Quantity of ethanol per day (g) ^a mean (SD)	288.4 (175.4)	293.7 (158.5)	321.8 (187.9)
Years since alcohol-related problems occurred, mean (SD)	9.9 (8.8)	10.1 (7.6)	9.0 (8.3)
Cigarettes per day, mean (SD)	17.8 (10.9)	13.3 (12.7)	18.5 (12.6)
Family history positive for alcoholism (%)	77.8	81.6	84.6
Previous treatments for alcoholism (%)	51.9	53.1	53.9
Monthly income (in R\$, Brazilian currency), mean (SD)	796 (716)	738 (672)	1013 (1165)
Plasma GGT, U/l (reference range 8–61), mean (SD)	114 (132)	94 (71)	110 (127)
Plasma ALT, U/l (reference range < 41), mean (SD)	38.0 (25.7)	39.8 (28.8)	32.3 (21.6)
Plasma AST, U/L; (reference range < 37) mean (SD)	42.0 (34.0)	44.9 (34.5)	40.1 (36.4)
Plasma MCV, f/l (reference range 80–100), mean (SD)	95.6 (6.9)	95.0 (7.3)	95.2 (6.5)
SADD, mean (SD)	27.1 (8.4)	29.7 (8.3)	29.8 (8.8)
OCDS, mean (SD)	47.9 (12.6)	50.9 (13.6)	50.7 (13.5)
Ham-D, mean (SD)	10.5 (7.0)	10.7 (6.8)	9.8 (7.0)

^aIndicates alcohol usage during the last 3 months preceding the first day of the study. GGT: gamma-glutamyl transferase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; MCV: mean cellular volume; SADD: Short Alcohol Dependence Data; OCDS: Obsessive-Compulsive Drinking Scale; Ham-D: Hamilton Depression Rating Scale; SD: standard deviation.

groups (Yates's correction = 1.59, 1 df, $P = 0.21$). Similarly, the proportion of subjects who persisted completely abstinent until the eighth week was statistically different among the groups ($\chi^2_{(2)} = 8.79$, $P = 0.01$). After Yates's correction, the topiramate group again revealed higher proportion of abstinent participants than the placebo group (Yates's correction = 7.36, 1 df, $P < 0.01$), with no significant differences between naltrexone and placebo (Yates's correction = 0.61, 1 df, $P = 0.43$) or topiramate and naltrexone groups (Yates's correction = 2.85, 1 df, $P = 0.09$). At the end of this study (12th week), although the proportion of subjects completely abstinent was higher in the topiramate group, this difference was no longer statistically significant ($\chi^2_{(2)} = 4.98$, $P = 0.08$).

The mean time to first relapse among the groups was statistically different, $F_{(2, 152)} = 4.65$, $P = 0.01$ (ANOVA), as shown in Table 3. After Bonferroni correction, the topiramate group revealed higher time to first relapse than the placebo group (mean difference = 2.8 weeks, $P = 0.01$). There were no significant differences between the topiramate and naltrexone groups (mean differ-

ence = 2.1 weeks, $P = 0.10$), or between the naltrexone and the placebo groups (mean difference = 0.7 weeks, $P > 0.99$).

A similar pattern of results was seen for CAD. There were significant differences among the groups ($F_{(2, 152)} = 3.91$, $P = 0.02$); the topiramate group showed higher cumulative abstinence duration than the placebo group (mean difference = 2.6 weeks, $P = 0.02$), with no significant differences between the naltrexone and topiramate groups (mean difference = 1.6 weeks, $P = 0.32$) or between the naltrexone and the placebo groups (mean difference = 1.0 weeks, $P = 0.83$).

Considering the heavy drinking weeks (number of weeks in which the use of ethanol was higher than 90 g), there were significant differences among the groups, $F_{(2, 152)} = 3.82$, $P = 0.02$. After Bonferroni correction, the topiramate group showed fewer mean number of weeks of heavy drinking than the placebo group (mean difference = 2.4 weeks, $P = 0.02$) with no significant differences between the topiramate and the naltrexone groups (mean difference = 1.6 weeks, $P = 0.27$), or between

Table 3 Drinking outcome variables at the end of the study of subjects treated with naltrexone, topiramate or placebo and participation in Alcoholics Anonymous groups (AA).

Variables	Placebo (n = 54)	Naltrexone (n = 49)	Topiramate (n = 52)	Post-hoc tests (Bonferroni/Yates's correction)
Time to first relapse (in weeks), mean (SD)	5.0 (4.8)	5.7 (4.7)	7.8 (4.9)	Topiramate versus placebo ($P = 0.01^*$) Topiramate versus naltrexone ($P = 0.10$) Naltrexone versus placebo ($P > 0.99$)
Cumulative abstinence duration (in weeks), mean (SD)	5.6 (4.8)	6.6 (4.9)	8.2 (4.5)	Topiramate versus placebo ($P = 0.02^*$) Topiramate versus naltrexone ($P = 0.32$) Naltrexone versus placebo ($P = 0.83$)
Heavy drinking weeks, mean (SD)	5.9 (4.8)	5.0 (5.1)	3.4 (4.5)	Topiramate versus placebo ($P = 0.02^*$) Topiramate versus naltrexone ($P = 0.27$) Naltrexone versus placebo ($P = 0.98$)
Remaining continuously abstinent (%)				
at 4th week*	42.6	53.1	67.3	Topiramate versus placebo ($P = 0.01^*$) Topiramate versus naltrexone ($P = 0.21$) Naltrexone versus placebo ($P = 0.39$)
at 8th week*	31.5	40.8	61.5	Topiramate versus placebo ($P < 0.01^*$) Topiramate versus naltrexone ($P = 0.09$) Naltrexone versus placebo ($P = 0.43$)
at 12th week	27.8	28.6	46.2	–
Plasma GGT, U/l; mean (SD)	86.9 (124.8)	63.0 (63.0)	68.0 (91.5)	–
OCDS, mean (SD)	21.9 (8.6)	22.4 (10.3)	22.4 (9.4)	–
Participation in AA* (%)	7.4	4.1	19.2	Topiramate versus placebo ($P = 0.13$) Topiramate versus naltrexone ($P = 0.04^*$) Naltrexone versus placebo ($P = 0.76$)

* $P < 0.05$. GGT: gamma-glutamyl transferase; OCDS: Obsessive-Compulsive Drinking Scale. SD: standard deviation.

the placebo and the naltrexone groups (mean difference = 0.9 weeks, $P = 0.98$).

With regard to the GGT, there was a marked decline from beginning to end of the study, but no significant difference among the groups at end of study ($F = 0.87$, $P = 0.42$). Similarly, mean scores on OCDS declined during the study with no between-group differences at end of the study ($F = 0.03$, $P = 0.97$).

Survival analysis and Cox regression (ITT)

As shown in Fig. 2, the proportion of subjects who remained without relapse was higher in the topiramate group than in the placebo group throughout the 90 days of treatment ($P = 0.02$, log-rank test). However, there were no statistically significant differences between the naltrexone and topiramate groups ($P = 0.06$, log-rank test) or between the naltrexone and placebo groups ($P = 0.64$, log-rank test).

Participation in AA groups was recommended for all subjects in this study, but was not an obligatory condition to take part in the study. Nevertheless, there was a significant difference among the groups on participation in AA self-help groups ($\chi^2_{(2)} = 7.01$, $P = 0.03$). After Yates's correction, the topiramate group showed a higher proportion of participants in AA than did the naltrexone group

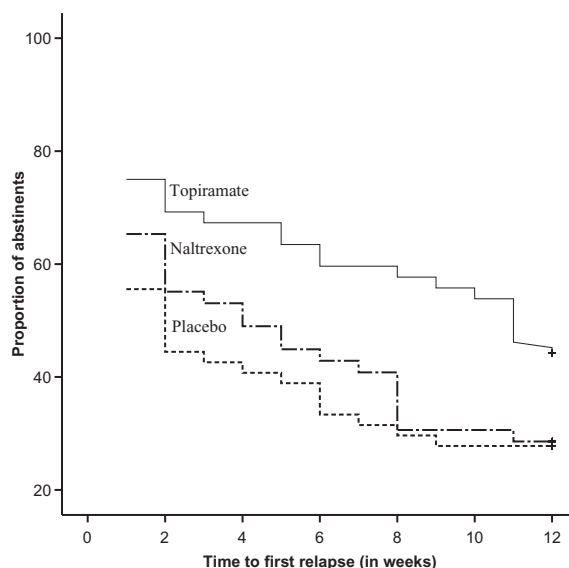


Figure 2 Survival curve of time to first relapse for subjects randomized to topiramate, naltrexone or placebo

(Yates's correction = 4.18, 1 df, $P = 0.04$), with no significant difference between the placebo and topiramate (Yates's correction = 2.28, 1 df, $P = 0.13$) or placebo and naltrexone groups (Yates's correction = 0.09, 1 df,

Table 4 Side effect profile of subjects receiving placebo, naltrexone or topiramate.

Clinical event	Placebo (n = 54) (%)	Naltrexone (n = 49) (%)	Topiramate (n = 52) (%)
Nothing reported	51.9	57.1	44.2
Somnolence	13.0	20.4	13.5
Insomnia	5.6	10.2	9.6
Fatigue	3.7	4.1	3.9
Paraesthesias*	3.7	2.0	11.5
Nausea	7.4	4.1	5.8
Diarrhoea	5.6	0	1.9
Constipation	3.7	2.0	0
Loss of appetite	3.7	0	7.7
Dizziness	1.9	4.1	5.8
Pruritus	1.9	4.1	1.9

* $\chi^2 = 4.83$, 2 df, $P = 0.09$.

$P = 0.76$). Because of this higher AA participation rate in the topiramate group, AA participation was entered as a covariate in the Cox proportional-hazards regression model for time to first relapse. Participation in AA did not predict survival time reliably after adjustment for medication condition [Wald = 0.01, 1 df, $P = 0.96$, odds ratio (OR) = 1.02, confidence interval (CI) = 0.52–1.98]. However, the use of topiramate did predict survival time reliably after adjustment for participation in AA (Wald = 4.05, 1 df, $P = 0.04$, OR = 0.61, CI = 0.38–0.99). The odds ratio of 0.61 means that use of topiramate decreased the odds of failing by 39% compared to placebo. Naltrexone use did not predict survival time reliably after adjustment for participation in AA (Wald = 0.14, 1 df, $P = 0.71$, OR = 0.92, CI = 0.58–1.45).

Safety and tolerability

The profile of side effects by groups is shown in Table 4. There were no statistically significant differences among the groups. Although paraesthesia was reported more frequently by patients in the topiramate group, it was not significantly different from the other groups.

Integrity of the double-blind trial

Both study patients and research staff were queried as to which pharmacological treatment they thought each patient had received. Overall, researchers were able to differentiate active treatment (naltrexone or topiramate) correctly from placebo treatment in 33.6% of cases. Among subjects, 27% were able to differentiate active treatment (naltrexone or topiramate) correctly from placebo treatment. This included 27.8% of placebo

subjects, 24.5% of the naltrexone group and 28.9% of the topiramate subjects. These differences were not significant ($\chi^2 = 0.26$, $P = 0.88$).

Power analysis

Our sample was unable to show any differences between the two active medications (topiramate and naltrexone). In fact, comparisons between two active medications would be expected to yield a smaller effect size than those between an active drug and placebo. The PASS statistical program was used in a one-way ANOVA to calculate power of the present sample size to detect differences between topiramate and naltrexone on the mean time to first relapse measure. The total sample of 155 subjects achieved 75% power to detect differences among the means of the three groups versus the hypothesis of equality among the means, using an F -test with a 0.05 significance level, β factor estimated as 25%, and a common standard deviation within each group of 4.9 weeks. A sample size of 58 per group would be needed to detect the topiramate versus naltrexone effects observed with power of 80%.

DISCUSSION

Topiramate was significantly more effective than placebo in delaying time to the first alcohol drinking relapse, increasing treatment retention and abstinence duration during a 12-week randomized efficacy evaluation and reducing mean duration of heavy drinking. Cox regression analysis revealed that topiramate reduced the odds of relapse by 39%, even after adjustment for participation in AA self-help groups. Although there were no significant differences between topiramate and naltrexone on a variety of outcome measures, topiramate showed noticeable trends toward superiority over naltrexone on several critical measures of drinking including time to first relapse, cumulative abstinence duration and heavy drinking weeks. A power analysis suggested that topiramate versus naltrexone differences may have been detected with a modestly larger sample size (174 versus 155).

The current findings support previous clinical studies which have shown that topiramate at doses up to 300 mg/day holds considerable promise for the treatment of alcoholism [11–15]. Recently, Miranda *et al.* [33], demonstrated in an open-label study that relatively low doses of topiramate (200 mg/day) were effective for patients with both a history of treatment for alcoholism and concurrent psychiatric problems for which they were receiving medications. Thus, this medication may have fairly wide applicability to the alcoholic population.

Not only did topiramate prove to be efficacious, it also has a favourable side-effect profile. In the present study,

there were no differences among topiramate, naltrexone and placebo in terms of side effects. The most common adverse effects of topiramate were paraesthesia, anorexia and memory and concentration difficulties, but a slow titration to the ceiling dose can minimize these effects and increase its tolerability significantly [7,34].

Subjects who received topiramate had a higher rate of participation in AA groups compared with subjects in either of the other treatment groups. This interesting observation suggests that an efficacious medication treatment may, secondarily, promote better adherence to recommendations of care providers, including the recommendation to participate in AA self-help programmes.

The lack of significant effects for naltrexone versus placebo in the present trial are consistent with mixed reports of its efficacy as a treatment for alcohol dependence [18,19]. It is possible that significant effects would have been detected if sample sizes were larger or if other criteria for relapse had been used. Nevertheless, the results support a relatively smaller effect for naltrexone than for topiramate. Our study did not evaluate the efficacy of the drugs prescribed by specific types of drinkers, so that no patient-treatment-matching hypotheses could be tested. However, it is tempting to propose that topiramate may have broader efficacy than naltrexone by reducing impulsiveness, anxiety and dysphoria related to the withdrawal of alcohol, while naltrexone may be more useful specifically for craving reduction in alcoholics, who manifest high desire for drinking. Differential efficacy in various drinker subgroups could help to explain why there were no significant differences between these two medications on primary clinical outcomes in a heterogeneous group of alcoholics.

Some limitations of the study need to be considered. [1] The number of dropouts was high in the three treated groups, possibly because of the limited structure and psychosocial treatment entailed in the community-based programmes where the study was carried out. However, this approach to trial design can also be viewed as a strength, as it enhances external validity. [2] All participants in this study were asked to take two capsules per day to maintain medication blinding. It is possible that a once-per-day medication regimen would result in better patient adherence. If this is true, the naltrexone group may have been at a disadvantage in the study as this medication does not, in fact, require twice-daily dosing. [3] Throughout the study, naltrexone was administered at a fixed daily dose of 50 mg, which is the traditional dose used in studies on the efficacy of naltrexone for the treatment of alcohol dependence. However, more recent trials [35] have suggested that a daily naltrexone dose of 100 mg could be more efficacious; [4] additional significant effects may have been detected with a larger sample size.

In summary, this study contributes important new data on the efficacy of topiramate in the treatment of alcohol dependence. Although topiramate has not been approved for the treatment of alcoholism as yet, this study and others have demonstrated that the medication is superior to placebo in improving outcome measures associated with chronic alcohol misuse. In addition this study is, to our knowledge, the first randomized, double-blind, parallel group trial to compare topiramate versus naltrexone in the treatment of alcohol-dependent outpatients. The study also provides some support for the superiority of topiramate over naltrexone for this purpose, although more research with larger sample sizes will be needed to verify these observations.

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