



Effects of topiramate or naltrexone on tobacco use among male alcohol-dependent outpatients[☆]

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ABSTRACT

Background: A high smoking prevalence has been registered among alcoholics. It has been pointed out that alcoholic smokers may have a more severe course and greater severity of alcoholism. This study aims at comparing smoking and non-smoking alcoholics in terms of treatment outcomes and verifying the efficacy of topiramate and naltrexone to decrease the use of cigarettes among alcoholic smokers.

Methods: The investigation was a double-blind, placebo-controlled, 12-week study carried out at the University of São Paulo, Brazil. The sample comprised 155 male alcohol-dependent outpatients (52 non-smokers and 103 smokers), 18–60 years of age, with an International Classification of Diseases (ICD-10) diagnosis of alcohol dependence. After a 1-week detoxification period, the patients randomly received placebo, naltrexone (50 mg/day) or topiramate (up to 300 mg/day). Only the alcoholic smokers who adhered to the treatment were evaluated with reference to the smoking reduction.

Results: Cox regression analysis revealed that the smoking status among alcoholics increased the odds of relapse into drinking by 65%, independently of the medications prescribed, using the intention-to-treat method. Topiramate showed effectiveness to reduce the number of cigarettes smoked when compared to placebo among adherent patients (mean difference = 7.91, $p < 0.01$). There were no significant differences between the naltrexone group and the placebo group.

Conclusions: The results of this study confirm that the treatment is more challenging for smoking alcoholics than for non-smoking ones and support the efficacy of topiramate in the smoking reduction among male alcoholic smokers who adhered to the treatment.

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1. Introduction

Global consumption of cigarettes has been rising steadily since manufactured cigarettes were introduced at the beginning of the 20th century. There are more than 1 billion smokers over the world (World Bank, 1999) and in Brazil approximately 20% of the people over 15-year-old smoke (Carlini et al., 2001). Also, about 9% of the adult population can be considered nicotine dependent and almost 200,000 annual deaths due to smoking-related problems have been reported in Brazil (Brasil, 2004).

One of the groups with high risk of frequent and heavy smoking consists of alcohol-dependent individuals. The prevalence of smoking among treatment-seeking alcohol dependent patients has

been reported to be as high as 80% (Littleton et al., 2007; Martin et al., 2006). In fact, alcohol dependents smoke regularly and they usually reveal greater alcohol consumption than non-smoking alcoholics (Daepfen et al., 2000; Marks et al., 1997). Furthermore, most alcoholic patients who smoke continue to report a high level of cigarettes smoked during the withdrawal from alcohol as a way to cope with unpleasant symptoms (Meyerhoff et al., 2006; Prendergast et al., 2002). Alcohol and nicotine act synergistically in different people so that those who drink and smoke drink more than non-smokers, and drinkers smoke more than non-drinkers (Hertling et al., 2005; Berggren et al., 2007). In addition, it has been evaluated that the combined health risk of smoking and alcohol consumption may be 50% higher than the sum of their independent risks (Bien and Burge, 1990).

In reality, behavioral studies suggest a role for nicotinic acetylcholine receptors (nACh) in the mediation of alcohol sensitivity. There is evidence that alcohol may excite ventral tegmental area (VTA) neurons through nACh receptors, facilitating the dopaminergic activity and, consequently, improving rewarding effects (Blomqvist et al., 2002). Also, there seems to be an up-regulation of

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nACh receptors in situations where there is chronic nicotine intake, increasing the likelihood of alcohol consumption. Therefore, this implies that smoking enhances the pleasurable effects of alcohol intake. On the other hand, it seems that alcohol usage potentiates the activity of certain subunits of the acetylcholine receptors and this can cancel out nicotine's own ability to desensitize them, increasing the smoking behavior (Johnson, 2004). Furthermore, there seems to be genetic factors contributing to concurrent misuse of alcohol and nicotine (Li et al., 2005).

Although some alcoholics under treatment do not want to quit smoking, several studies have contended that many of them are willing to consider this possibility (Ellingstad et al., 1999; Sobell et al., 2002). Unfortunately, some alcohol treatment programs have been reluctant to promote smoking cessation, presumably because of the lack of interest among patients or negative effects on alcohol treatment outcomes (Burling et al., 1997; Joseph et al., 2004; Schmidt and Smolka, 2001). In fact, Palfai et al. (2000) reported that nicotine deprivation can be related to increased urges to drink and intrusive thoughts regarding alcohol in a hazardous drinking sample. Despite this, there is no strong scientific evidence that smoking cessation management during the treatment for alcoholism hinders the therapeutic outcomes (Stotts et al., 2003). In a study by Cooney et al. (2003), which aimed at evaluating alcohol-dependent smokers on measures of reactivity to alcohol cue exposure during nicotine deprivation, increased urges to drink were not observed. Other clinical research studies of patients in treatment for alcohol misuse in which smoking cessation was a targeted outcome have found that smoking cessation improved alcohol abstinence, or at least did not harm sobriety (Friend and Pagano, 2005; Lemon et al., 2003; Martin et al., 1997; Sullivan and Covey, 2002). Therefore, initiating smoking cessation interventions during the treatment of alcohol dependence may not jeopardize abstinence from alcohol.

These controversies reveal that further research is warranted to evaluate whether tobacco cessation is related to the maintenance of alcohol abstinence or to relapse. Also, a type of pharmacological therapy which deals with both conditions simultaneously would be extremely welcome, given the great discussion whether the management focused on smoking cessation must begin during or after the treatment for alcoholism among alcoholic smokers.

Our study was designed to investigate whether smoking and non-smoking alcoholics differ in terms of alcohol dependence and alcohol treatment outcome. Among the smokers, we also examined whether topiramate or naltrexone differentially influenced the number of cigarettes smoked during follow-up compared to placebo. To date, we are aware of only one pharmacological trial that has evaluated the influence of medications prescribed for alcohol-dependent patients on smoking reduction (Johnson et al., 2005).

2. Methodology

2.1. Participants

This study was part of a pharmacological trial, where the efficacy of topiramate and naltrexone was compared among alcohol-dependent outpatients, in a randomized, double-blind, placebo-controlled study. Participants were 175 male patients, 18–60 years of age, with an International Classification of Diseases (ICD-10, World Health Organization, 1992) diagnosis of alcohol dependence who enrolled as outpatients in the Assistance Sector of the Interdisciplinary Group of Studies on Alcohol and Drugs at the University of São Paulo—a specific clinic for the treatment of males with alcohol and/or any other kind of drug misuse. The selected patients needed to show problems associated with alcohol misuse for at least 2 years. All diagnoses were made by experienced psychiatrists who did not participate in this study.

The most common reason for refusal was the patient's unwillingness to take part in a research with its extra burdens and lack of interest in taking medications. The reasons for exclusion were: serious clinical coexisting diseases (e.g., inadequately controlled diabetes, cardiac failure, alcoholic cirrhosis), previous treatment with naltrexone or topiramate within 6 months of randomization, any other drug dependence (except nicotine), and concomitant psychiatric disorders that might require specific drug treatment.

2.2. General procedures

This study was approved by the Ethics Committee of the Clinical Hospital of the University of São Paulo, Brazil. A written informed consent was obtained from each patient during the first week of the study.

Participants were informed about the study objectives, the nature of the treatment provided, the profile of medications tested and that the medications would be randomly given. The methodology of this randomized, double-blind and placebo-controlled study was described previously (Baltieri et al., 2008). In summary, patients screened for this research were randomly divided into three groups (placebo, naltrexone and topiramate). All patients received two identical capsules a day during 12 weeks. In the naltrexone group, one capsule was filled with placebo and the other with naltrexone—50 mg. In the topiramate group, the two capsules contained escalating doses of this medication—25, 50 or 100 mg in each week, increasing to 300 mg/day by week 8. In this group, from week 8 to end of week 12, the dose of topiramate remained 300 mg/day (Table 1). In the placebo group, all capsules contained placebo. The capsules were big enough to contain all tablets of topiramate; therefore, all capsules in each treatment group were identical. At each visit, both the returned packages and the calendar-based pill-taking schedule were used to calculate pill count and monitor compliance. All capsules were manufactured by the Pharmacy Sector at the Psychiatric Institute of the Clinical Hospital of the University of São Paulo, Brazil.

The patients were assured that they would not be withdrawn from the service if they relapsed or failed to comply with the medication and that they could choose to leave the programme at any time. In fact, they could participate in other types of treatment available in our service if they decided to discontinue the research.

All patients were also encouraged to participate in Alcoholics Anonymous Groups (AA), but this was not an obligatory condition of taking part of this study.

Also, at each appointment, all patients received standardized brief cognitive behavioral interventions provided by their doctors. The overall goal of these interventions was to increase the person's ability to cope with high-risk situations that could precipitate alcohol relapses. At each visit, the drinking behavior and the number of cigarettes smoked were reviewed and the medication compliance and motivation for change were improved using motivational interviewing strategies. Although no specific management for smoking cessation was applied in this study, the number of cigarettes smoked was assessed during the research.

The patients were instructed to monitor good and bad daily situations during treatment and this was discussed with their doctors and, when possible, related to the drinking behavior. 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.

2.3. Measures

As this research was not designed specifically to measure smoking behavior, we neither collect breath carbon monoxide level nor ascertain nicotine withdrawal status. Eligible subjects were enrolled at the beginning of week 1, following a review of the hematologic and biochemical tests. We also assessed subjects on safety measures including vital signs, weight, adverse effects, and concomitant medication use. The Timeline Followback (TLFB) method (Sobell et al., 1996) was used to quantify self-reported drinking and smoking. This method uses a calendar and memory aids to facilitate retrospective estimates of daily drinking and smoking over a certain period (Stotts et al., 2003). As the patients were assessed 8 times during the trial at weeks 1, 2, 3, 4, 6, 8, 10 and 12 after the baseline assessment, this method was used at each appointment. We could assess the number of cigarettes smoked as well as the quantity of alcohol used by each patient during the study. Participants who smoked 15 or more cigarettes a day were considered alcoholic smokers. In fact, this was the smallest number of cigarettes smoked by our patients (alcoholic smokers), whereas the largest number was 40 cigarettes a day. Non-smokers were defined as those who had never used nicotine or those who had not used this substance during the last 3 months. From our total eligible sample, only 12 (6.86%) patients were ex-smokers. None of the patients reported occasional smoking.

In addition, all patients were evaluated with the Short Alcohol Dependence Data (SADD) (Raistrick et al., 1983) at the start of this research, and the Hamilton Depression Rating Scale (Ham-D) (Hamilton, 1960), and the Obsessive-Compulsive Drinking Scale (OCDS) (Anton et al., 1995) at the start and at the end of this study. For all patients, abstinence from alcohol and quantity of cigarettes smoked were evaluated on the basis of the patient's self-report and by interviewing a family member, whenever possible. Of the eligible subjects, 111 (63.43%) brought along at least one family member during the appointments. Alcohol abuse hepatic indices, such as gamma glutamyl-transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and mean cellular volume (MCV), were measured at the start and at the end of the study.

2.4. Outcome measures

For the proposals of this study, we have firstly verified differences between alcoholic non-smokers and alcoholic smokers in terms of sociodemographic fea-

Table 1
Topiramate dose-escalating schedule.

Weeks	Morning capsule (contents in grams)	Night capsule (contents in grams)	Total dose (mg)
1	0 mg (placebo tablet)	1 tablet of 25 mg	25
2	0 mg (placebo tablet)	2 tablets of 25 mg	50
3	1 tablet of 25 mg	2 tablets of 25 mg	75
4	2 tablets of 25 mg	2 tablets of 25 mg	100
5	2 tablets of 25 mg	1 tablet of 100 mg	150
6	1 tablet of 100 mg	1 tablet of 100 mg	200
7	1 tablet of 100 mg	1 tablet of 100 mg and 2 tablets of 25 mg	250
8–12	1 tablet of 100 mg and 2 tablets of 25 mg	1 tablet of 100 mg and 2 tablets of 25 mg	300

tures, severity of alcohol dependence, alcohol abuse hepatic indices and adherence to the treatments provided. With respect to the drinking behavior, we have analyzed differences between both groups of alcoholics in terms of time to first relapse, after adjustment for the different medications used. In our study, time to first relapse was defined as the period (in weeks) from the start of the treatment to the first consumption of any quantity of ethanol. In this analysis, we have used 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. Therefore, patients who missed a visit or withdrew from the study were deemed to be non-abstinent, since they had taken at least one dose of the trial medication.

Next, we evaluated only the group of smoking alcoholics in terms of number of cigarettes smoked during this research. Only the participants who completed the study have been investigated with respect to smoking reduction, because they adhered to all requirements of this study, including the correct usage of the medications prescribed.

In this research, three reasons for dropping out were considered, such as “refusal to continue” (the patient affirmed that he wanted to stop this type of treatment and try others), “protocol violation” (the patient used other psychopharmacological drugs during this study) and “premature discontinuation of the follow-up” (the patient gave up following the study and did not manifest any desire to be treated differently). Patients who did not attend follow-up and whose outcome was unknown were considered non-adherent.

2.5. Statistical analysis

For all statistical tests performed, differences between the two groups were accepted as significant if they achieved the 0.05 level with two-tailed tests. Data were analyzed using the SPSS 15 and Stata 9 statistical packages.

Parametric methods were applied when the observations within each group had an approximately normal distribution, according to the Levene's criteria. However, if the variances among variables were unequal, a non-parametric method was utilized.

2.5.1. Smoking and non-smoking alcoholics

Baseline differences between these two groups were determined using the parametric *t*-test or the non-parametric Mann–Whitney *U*-test for continuous variables. Categorical variables were compared by using the χ^2 -test. A multiple variance analysis (MANOVA) was also used because this piece of the research evaluated many dependent variables and only a univariate analysis could increase the chance of missing data.

2.5.2. Time to first relapse

As the alcoholic smokers and alcoholic non-smokers were treated with different medications, we used the *Cox Proportional Regression Analysis* for the adjustment of two independent variables or covariates (different types of alcoholics, according to the smoking status, and different types of medications prescribed) which could confound the dependent variable or “survival time” (time to first relapse). This method models event rate (time to first relapse) as a log-linear function of predictors or covariates.

2.5.3. Cigarettes smoked during the study

Considering only the group of alcoholic smokers, we evaluated differences in the number of cigarettes smoked between the start and the end of this study for each type of medication prescribed. Only the participants who adhered to this study were evaluated with respect to the possible variability of number of cigarettes smoked during the follow-up.

The *Wilcoxon signed rank sum test* has been applied to analyze differences in the mean number of cigarettes smoked between the start and the end of this research, within each subgroup of smoking alcoholics.

Finally, partial correlations to further evaluate the linear relationship between smoking (number of cigarettes per day at the end of the research) and alcohol abstinence (percentage of days abstinence), adjusting for baseline covariate (number of cigarettes used at the beginning of the study) were performed.

3. Results

3.1. Sample characteristics

Of the 175 eligible patients, 14 (8%) refused to participate in this study, and 6 (3.43%) were excluded due to coexisting diseases that could harm their suitable participation. Of the remaining 155 participants, 52 (33.55%) were non-smokers and 103 (66.45%) were smokers. The mean of cigarettes smoked per day among alcoholic smokers was 24.17 (6.68).

In Table 2, we described the baseline characteristics of each of the 6 subgroups of patients, according to the smoking status and the medications prescribed. During the analyses, we have compared the group of alcoholic smokers with the non-smokers as a whole to avoid Type I errors to multiple comparisons.

There were no significant differences between these two groups in terms of types of medications prescribed and socio-demographic aspects. Despite this, alcoholic smokers showed higher quantity of ethanol consumed per day (in grams) than non-alcoholic smokers (*U* Mann–Whitney = 1986, $p < 0.01$) (Table 2).

Also, there were no significant differences between both groups with reference to the following variables: years since alcohol-related problems occurred, family history for alcoholism, previous treatment for alcoholism, mean values of the alcohol abuse hepatic indices GGT, ALT and AST, and mean scores of the SADD, OCDS and Ham-D at baseline. However, smoking alcoholics demonstrated higher mean serum levels of MCV than non-smoking alcoholics ($t = 2.23$, 153 df, $p = 0.03$) (Table 2).

3.2. Baseline multivariate analysis

A 2×5 MANOVA was conducted, with the groups of alcoholic smokers and non-smokers as the independent variable, and the alcohol abuse hepatic indices (GGT, ALT, AST, MCV) and the quantity of ethanol consumed per day (in grams) obtained at the start of this study as the dependent variables. The overall MANOVA was significant, Pillai's $F(5,149) = 4.39$, $p < 0.01$, $\partial n^2 = 0.13$.

3.3. Outcome measures (intention to treat)

3.3.1. Time to first relapse. The group of non-smoking alcoholics showed longer time to first relapse than the group of smoking alcoholics (7.09 ± 4.98 versus 5.42 ± 4.84) and this difference was statistically significant ($t = 2.02$, 153 df, $p = 0.04$). Although the types of medications received by smoking and non-smoking alcoholics were not significantly different, the effect of each type of medication used could interfere in this result. Due to this, we carried out the *Cox Proportional-Hazards Regression Model* to control the effects of both variables – ‘types of alcoholics (smokers or non-smokers)’ and ‘types of medications prescribed’ – on the time to first relapse. According to the Wald criterion, the group of alcoholic smokers reliably predicted survival time negatively, after adjustment for the different medications prescribed (Wald = 4.93, 1 df, $p = 0.03$, OR = 1.65, CI = 1.06–2.56). On the other hand, according to

Table 2
Baseline characteristics.

Variables	Non-smokers				Smokers				p (between smokers and non-smokers groups)
	Naltrexone (n = 22)	Topiramate (n = 14)	Placebo (n = 16)	Total (n = 52)	Naltrexone (n = 27)	Topiramate (n = 38)	Placebo (n = 38)	Total (n = 103)	
Age, mean (SD)	43.09 (8.35)	47.14 (7.88)	41.12 (9.58)	43.58 (8.77)	44.89 (6.07)	44.92 (9.69)	44.34 (8.33)	44.69 (8.29)	t = 0.78, 153 df, p = 0.44
Race, n (%)									
White	13 (59.09)	10 (71.43)	12 (75)	35 (67.31)	21 (77.78)	28 (73.68)	26 (68.42)	75 (72.82)	$\chi^2 = 0.89$, 2 df, p = 0.64
Black	2 (9.09)	1 (7.14)	2 (12.50)	5 (9.61)	0	6 (15.79)	0	6 (5.82)	
Mixed races	7 (31.82)	3 (21.43)	2 (12.50)	12 (23.08)	6 (22.22)	4 (10.53)	12 (31.58)	22 (21.36)	
Marital status, n (%)									
Married	12 (54.55)	8 (57.14)	10 (62.50)	30 (57.69)	12 (44.45)	20 (52.63)	18 (47.37)	50 (48.54)	$\chi^2 = 2.64$, 2 df, p = 0.27
Single	4 (18.18)	3 (21.43)	3 (18.75)	10 (19.23)	6 (22.22)	7 (18.42)	3 (7.89)	16 (15.54)	
Separated/widowed	6 (27.27)	3 (21.43)	3 (18.75)	12 (23.08)	9 (33.33)	11 (28.95)	17 (44.74)	37 (35.92)	
Quantity of ethanol per day (in g) ^a , mean (SD)	249.95 (81.34)	258.86 (100.39)	275.75 (96.86)	260.29 (90.41)	339.93 (140.70)	341.26 (128.03)	304.63 (183.42)	327.34 (153.31)	U = 1986, p < 0.01**
Years since alcohol-related problems occurred, mean (SD)	10.73 (8.12)	10.29 (8.72)	10.06 (8.90)	10.40 (8.36)	9.52 (7.26)	8.58 (8.24)	9.76 (8.83)	9.26 (8.16)	t = 0.82, 153 df, p = 0.42
Family history positive for alcoholism, mean (SD)	18 (81.82)	13 (92.86)	13 (81.25)	44 (84.61)	22 (81.48)	31 (81.58)	29 (76.32)	82 (79.61)	$\chi^2 = 0.57$, 1 df, p = 0.45
Previous treatment for alcoholism, n (%)	11 (50)	8 (57.14)	10 (62.50)	29 (55.77)	15 (55.56)	21 (55.26)	18 (47.37)	54 (52.43)	$\chi^2 = 0.15$, 1 df, p = 0.69
Monthly income (in R\$, the Brazilian currency), mean (SD)	739.09 (658.49)	885.36 (1177.20)	1087.50 (982.77)	885.67 (915.37)	736.67 (695.47)	1060.79 (1173.01)	673.53 (539.75)	832.95 (871.41)	t = 0.35, 153 df, p = 0.73
Cigarettes per day, mean (SD)	0	0	0	0	23.70 (6.29)	24.87 (7.75)	23.82 (5.86)	24.17 (6.68)	U < 0.01, p < 0.01**
Plasma GGT, U/L; (reference range 8–61), mean (SD)	82.74 (53.22)	84.07 (86.58)	98.87 (68.52)	88.06 (67.16)	108.96 (80.64)	118.97 (138.55)	120.53 (151.18)	116.92 (130.13)	U = 2479, p = 0.45
Plasma AST, U/L; (reference range < 37), mean (SD)	43.14 (36.59)	28.43 (9.39)	31.40 (11.37)	35.65 (25.81)	46.58 (32.19)	44.49 (41.71)	46.35 (38.94)	45.72 (38.03)	U = 2253, p = 0.24
Plasma ALT, U/L; (reference range < 41), mean (SD)	44.77 (34.20)	33.71 (24.27)	39.07 (29.34)	40.06 (30.12)	35.48 (22.79)	31.76 (20.78)	37.54 (24.45)	34.86 (22.63)	t = 1.19, 153 df, p = 0.24
Plasma VCM, f/L; (reference range 80–100), mean (SD)	93.04 (5.83)	94.97 (8.07)	92.96 (5.59)	93.54 (6.38)	96.76 (8.16)	95.26 (5.98)	96.65 (7.20)	96.16 (6.99)	t = 2.23, 153 df, p = 0.03 [†]
SADD, mean (SD)	28.18 (4.93)	30.07 (7.74)	28.62 (8.03)	28.83 (6.70)	30.85 (7.35)	30.76 (7.02)	27.50 (8.19)	29.58 (7.65)	U = 2636, p = 0.87
OCDS, mean (SD)	52.32 (12.21)	49.50 (13.43)	48.31 (12.69)	50.33 (12.56)	49.78 (14.79)	51.18 (13.66)	47.78 (12.68)	49.58 (13.57)	t = 0.33, 153 df, p = 0.74
Ham-D, mean (SD)	10.09 (7.35)	9.57 (6.94)	11.37 (7.18)	10.34 (7.08)	11.22 (6.46)	9.89 (7.11)	10.74 (7.23)	10.55 (6.95)	t = 0.17, 153 df, p = 0.86

^a Indicates alcohol usage during the last 3 months preceding the first day of this 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.

[†] p < 0.05.

** p < 0.01.

Table 3Effects of smoking status and types of medications prescribed on the time to first relapse ($n = 155$, Cox regression).

Variables	B	SE	Wald	df	p	OR	CI (95%)
Smoking status	0.49	0.22	4.93	1	0.03*	1.65	1.06–2.56
Naltrexone group	0.02	0.23	<0.01	1	0.94	0.98	0.62–1.56
Topiramate group	0.52	0.25	4.49	1	0.03*	0.59	0.36–0.96

* $p < 0.05$.

the same criterion, the use of topiramate reliably predicted the survival time positively, after adjustment for the other types of medications used and the smoking status (Wald = 4.49, 1 df, $p = 0.03$, OR = 0.59, CI = 0.36–0.96). In this analysis the odds ratio of 1.65 means that the smoking status among alcoholics increased the odds of failing by 65%. Also, the odds ratio of 0.59 means that the use of topiramate decreased the odds of failing by 41% (Table 3).

The use of naltrexone and placebo did not predict survival time, after adjustment for other variables (use of topiramate and smoking status). The analysis involving the efficacy of these three medications was described elsewhere (Baltieri et al., 2008).

3.3.2. Adherence to the treatment. In Table 4, we described the baseline characteristics of the patients who adhered to this study. The findings were similar to those of the initial sample.

Thirty-two (61.54%) non-smoking alcoholics and 53 (51.46%) smoking alcoholics adhered to this treatment ($\chi^2 = 1.42$, 1 df, $p = 0.23$).

In fact, when we performed a binary logistic regression to adjust the effects of the types of medications prescribed and of types of alcoholics (smokers and non-smokers) on the adherence to this treatment, only the use of topiramate reliably predicted the outcome (Wald = 4.71, 1 df, $p = 0.03$, OR = 2.38, CI = 1.09–5.23). In spite of this, a test of full model with both predictors against a constant-only model was not statistically significant ($\chi^2 = 6.56$, 3 df, $p = 0.09$). The variance in group membership was extremely marginal, with Nagelkerke $R^2 = 0.06$. In this analysis, 44.3% of non-adherent patients and 72.9% of adherent participants were adequately classified. The overall success rate for prediction was 60%.

3.3.3. Variability in the number of cigarettes smoked among alcoholic smokers. Among the alcoholic smokers, 27 (26.22%) patients received naltrexone, 38 (36.89%) were prescribed topiramate and 38 (36.89%) used placebo at the start of this study (Table 2).

Considering each subgroup of alcoholic smokers individually, in accordance with the medications prescribed, it has been verified that 13 (48.15%) alcoholic smokers that received naltrexone, 13 (34.21%) smoking alcoholics that used topiramate, and 24 (63.16%) alcoholic smokers who were prescribed placebo dropped out of this research, and this difference was statistically significant ($\chi^2 = 6.38$, 2 df, $p = 0.04$). After Yates' Correction, there was a statistically significant difference between the subgroups of alcoholic smokers who received topiramate versus placebo (Yates' Correction = 5.27, 1 df, $p = 0.02$). There was no significant difference between the subgroups who received naltrexone versus placebo (Yates' Correction = 0.90, 1 df, $p = 0.34$), nor any reliable difference between the subgroups who used naltrexone versus topiramate (Yates' Correction = 0.76, 1 df, $p = 0.38$) in terms of dropout rates.

Evaluating only alcoholic smokers who adhered to the treatment, the difference between the number of cigarettes smoked at the start and at the end of this study was statistically significant, $F(2,50) = 6.38$, $p < 0.01$. In reality, smoking alcoholics who received naltrexone showed a mean reduction in 3.57 (6.33) cigarettes smoked per day, those smoking participants who received topiramate manifested a mean reduction in 9.20 (7.86) cigarettes smoked

per day, and the group of smokers who used placebo had a mean reduction in 1.29 (6.27) cigarettes smoked per day. After Bonferroni correction, we verified a significant difference between the subgroups who received topiramate versus placebo (mean difference = 7.91, $p < 0.01$). There was no significant difference between the subgroups that used naltrexone versus placebo (mean difference = 2.28, $p > 0.99$) nor between the subgroups that were prescribed topiramate versus naltrexone (mean difference = 5.63, $p = 0.06$).

We have used the Wilcoxon signed rank sum test to analyze differences in the mean number of cigarettes smoked between the start and the end of this research, within each subgroup of smoking alcoholics. Considering only those participants who complied with this treatment, there was a significant difference with respect to the mean number of cigarettes smoked within the topiramate subgroup (z test = -3.74 , $p < 0.01$). There was no significant difference within the naltrexone subgroup (z test = -1.89 , $p = 0.06$) nor within the placebo subgroup (z test = -0.69 , $p = 0.49$). (Table 5; Fig. 1).

As the association between the variables 'number of cigarettes smoked at the end of this study' and 'percentage of abstinence days' for each treatment condition could be high and statistically significant, we have performed partial correlations, adjusting for the variable 'the number of cigarettes smoked at the beginning of this study'. For those who received topiramate, the partial correlation between 'cigarettes per day' and 'percentage of days abstinent' was negative, but not statistically reliable ($r = -0.34$, $p = 0.10$). For those who received naltrexone or placebo, the partial correlations between those two variables were also negative and not statistically significant ($r = -0.34$, $p = 0.26$, naltrexone; $r = -0.09$, $p = 0.76$, placebo).

Considering all alcoholic smokers who participated in this study, only 9 (8.74%) were no longer smoking at the end of treatment. Six (5.83%) participants had received topiramate, 2 (1.94%) had used naltrexone, and 1 (0.97%) had been prescribed placebo. This difference was not statistically reliable ($\chi^2 = 4.21$, 2 df, $p = 0.12$). It is important to note that this analysis allowed for an investigation of all smokers (not just treatment completers), assuming that those who dropped out continued smoking.

3.3.4. Safety and tolerability. Adverse effects were rated as mild or moderate, and all resolved without specific medical intervention. No serious side effects were reported. The six most frequent side effects referred by patients who took topiramate, naltrexone or

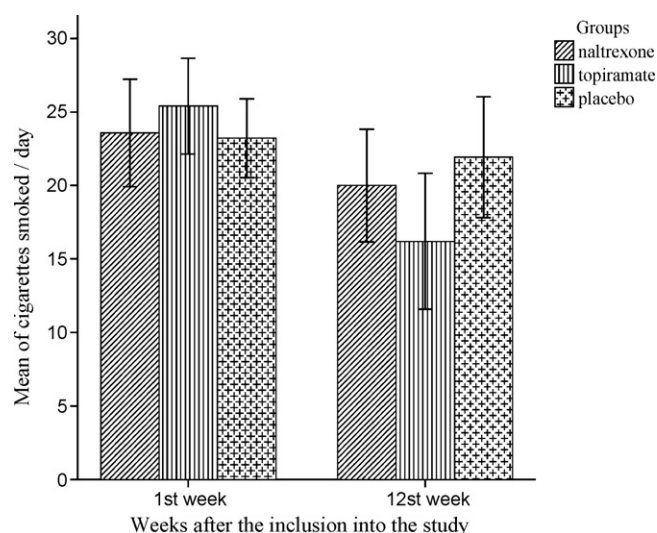


Fig. 1. Mean of cigarettes smoked among adherent alcoholic smokers receiving topiramate, naltrexone or placebo at the beginning and at the end of the study.

Table 4
Baseline characteristics among patients who adhered to this study.

Variables	Non-smokers				Smokers				<i>p</i> (between smokers and non-smokers groups)
	Naltrexone (<i>n</i> = 15)	Topiramate (<i>n</i> = 8)	Placebo (<i>n</i> = 9)	Total (<i>n</i> = 32)	Naltrexone (<i>n</i> = 14)	Topiramate (<i>n</i> = 25)	Placebo (<i>n</i> = 14)	Total (<i>n</i> = 53)	
Age, mean (SD)	43.93 (7.68)	46 (6.26)	41.89 (11.13)	43.87 (8.35)	45.36 (5.53)	46.92 (9.62)	44 (7.55)	45.74 (8.13)	<i>t</i> = 1.01, 83 df, <i>p</i> = 0.31
Race, <i>n</i> (%)									
White	9 (60)	5 (62.50)	7 (77.78)	21 (65.63)	10 (71.43)	21 (84)	11 (78.57)	42 (79.25)	$\chi^2 = 2.21$, 2 df, <i>p</i> = 0.33
Black	1 (6.67)	1 (12.50)	1 (11.11)	3 (9.37)	0	2 (8)	0	2 (3.77)	
Mixed races	5 (33.33)	2 (25)	1 (11.11)	8 (25)	4 (28.57)	2 (8)	3 (21.43)	9 (16.98)	
Marital status, <i>n</i> (%)									
Married	9 (60)	3 (37.50)	6 (66.67)	18 (56.25)	8 (57.14)	14 (56)	7 (50)	29 (54.72)	$\chi^2 = 1.39$, 2 df, <i>p</i> = 0.50
Single	4 (26.67)	3 (37.50)	1 (11.11)	8 (25)	2 (14.29)	5 (20)	2 (14.29)	9 (16.98)	
Separated/widowed	2 (13.33)	2 (25)	2 (22.22)	6 (18.75)	4 (28.57)	6 (24)	5 (35.71)	15 (28.30)	
Quantity of ethanol per day (in g) ^a , mean (SD)	258.13 (77.63)	285.25 (88.69)	265.89 (87.12)	267.09 (81.13)	314.29 (93.03)	317.12 (89.14)	338.71 (192.95)	322.07 (123.45)	<i>t</i> = 2.24, 83 df, <i>p</i> = 0.03 [*]
Years since alcohol-related problems occurred, mean (SD)	9.67 (7.51)	9.75 (8.81)	7.89 (8.34)	9.19 (7.85)	11.36 (8.25)	10.80 (9.26)	7.14 (6.78)	9.98 (8.43)	<i>t</i> = 0.43, 83 df, <i>p</i> = 0.67
Family history positive for alcoholism, mean (SD)	12 (80)	8 (100)	6 (66.67)	26 (81.25)	13 (92.86)	21 (84)	10 (71.43)	44 (83.02)	$\chi^2 = 0.04$, 1 df, <i>p</i> = 0.84
Previous treatment for alcoholism, <i>n</i> (%)	8 (53.33)	4 (50)	4 (44.44)	16 (50)	8 (57.14)	11 (44)	7 (50)	26 (49.06)	$\chi^2 < 0.01$, 1 df, <i>p</i> = 0.93
Monthly income (in R\$, the Brazilian currency), mean (SD)	550 (385.45)	724.37 (971.87)	1077.78 (1090.33)	742.03 (798.64)	838.57 (783.77)	976.40 (1151.93)	548.57 (397.14)	826.98 (914.92)	<i>t</i> = 0.43, 83 df, <i>p</i> = 0.66
Cigarettes per day, mean (SD)	0	0	0	0	23.57 (6.33)	25.40 (7.89)	23.21 (4.64)	24.34 (6.72)	<i>U</i> < 0.01, <i>p</i> < 0.01 ^{**}
Plasma GGT, U/L (reference range 8–61), mean (SD)	71.02 (39.79)	88 (97.77)	82.56 (62.35)	78.51 (62.70)	115.29 (78.85)	114.28 (130.99)	123.07 (114.48)	116.87 (112.98)	<i>U</i> = 669, <i>p</i> = 0.10
Plasma AST, U/L (reference range < 37), mean (SD)	45.80 (43.05)	26.87 (8.53)	27.89 (10.26)	36.03 (31.11)	51.29 (34.71)	44.72 (47.73)	50.79 (33.97)	48.06 (40.64)	<i>t</i> = 1.44, 83 df, <i>p</i> = 0.15
Plasma ALT, U/L (reference range < 41), mean (SD)	48.47 (40.22)	31 (24.98)	32.33 (17.94)	39.56 (32.04)	33.14 (21.99)	33.72 (22.99)	44.93 (32.52)	36.53 (25.60)	<i>t</i> = 0.48, 83 df, <i>p</i> = 0.63
Plasma VCM, f/L (reference range 80–100), mean (SD)	92.55 (6.15)	92.86 (6.81)	93.33 (4.64)	92.85 (5.76)	96.36 (9.30)	94.66 (5.78)	98.70 (5.38)	96.17 (6.86)	<i>t</i> = 2.30, 83 df, <i>p</i> = 0.03 [*]
SADD, mean (SD)	27.47 (5.64)	33.75 (5.06)	28.22 (8.89)	29.25 (6.90)	29.50 (7.06)	30.32 (7.20)	25.43 (7.09)	28.81 (7.29)	<i>t</i> = 0.27, 83 df, <i>p</i> = 0.78
OCDS, mean (SD)	50.80 (12.59)	51.50 (10.69)	52.44 (11.13)	51.44 (11.39)	47.43 (14.97)	50.28 (13.78)	45 (14.41)	48.13 (14.16)	<i>t</i> = 1.12, 83 df, <i>p</i> = 0.27
Ham-D, mean (SD)	10.40 (7.69)	9.50 (7.80)	9.11 (7.10)	9.81 (7.33)	9.64 (4.96)	9.16 (6.82)	8.14 (4.64)	9.02 (5.77)	<i>t</i> = 0.55, 83 df, <i>p</i> = 0.58

^a Indicates alcohol usage during the last 3 months preceding the first day of this 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.

^{*} *p* < 0.05.

^{**} *p* < 0.01.

Table 5
Mean of cigarettes smoked among adherent alcoholic smokers during the treatment.

Groups of medication	Mean number of cigarettes smoked at the start of the treatment	Mean number of cigarettes smoked at the end of the treatment	Differences in cigarettes smoked between the start and the end of the treatment	Test (Wilcoxon)	<i>p</i>
Naltrexone (<i>n</i> = 14)	23.57 (6.33)	20 (5.55)	3.57 (6.33)	<i>z</i> = −1.89	0.06
Topiramate (<i>n</i> = 25)	25.40 (7.89)	16.20 (11.21)	9.20 (7.86)	<i>z</i> = −3.74	<0.01**
Placebo (<i>n</i> = 14)	23.21 (4.64)	21.93 (7.11)	1.29 (6.27)	<i>z</i> = −0.69	0.49
Test	<i>H</i> = 0.51, 2 <i>df</i> ^a	<i>H</i> = 4.83, 2 <i>df</i> ^a	<i>F</i> (2,50) = 6.38 ^b	–	–
<i>p</i>	0.78	0.09	<0.01**	–	–

^a Kruskal–Wallis test.

^b ANOVA.

** *p* < 0.01.

placebo were (1) somnolence (13.5% versus 57.1% versus 13%), (2) insomnia (9.6% versus 10.2% versus 5.6%), (3) paraesthesias (11.5% versus 2% versus 3.7%), (4) nausea (5.8% versus 4.1% versus 7.4%), (5) loss of appetite (7.7% versus 0% versus 3.7%) and (6) fatigue (3.9% versus 4.1% versus 3.7%). No differences showed statistical significance.

3.3.5. Power analysis. The PASS statistical program was used in a one-way ANOVA to calculate the power of the present sample size to detect distinctions among the three groups of adherent alcoholic smokers who received topiramate, naltrexone or placebo with reference to the mean difference in the number of cigarettes smoked between the start and the end of this research. The total sample comprised by adherent participants (*n* = 53) achieved an effect size of 53% and power of 87% 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 13% and a common standard deviation within each group of 6.3 cigarettes.

4. Discussion

In this study, alcoholic smokers demonstrated a higher quantity of ethanol consumption before the treatment and worse parameter of the alcohol abuse hepatic index MCV than non-smoking alcoholics. In addition, Cox regression analysis revealed that the smoking status among alcoholics increased the odds of relapse to drinking by 65%, even after adjustment for the different medications used. Considering only the group of alcoholic smokers that remained in this study, the patients who received topiramate, but not naltrexone, showed significantly greater reduction in the number of cigarettes smoked than those who were prescribed placebo.

The current findings support previous clinical studies which have shown that alcoholic smokers show higher rates of alcohol consumption than non-smoking alcoholics (Berggren et al., 2007; Meyerhoff et al., 2006; Romberger and Grant, 2004) and that topiramate shows considerable promise for the treatment of comorbid alcohol and nicotine misuse (Johnson et al., 2005). Some other studies have verified that topiramate can be an important medication for the treatment of alcohol dependence (Johnson et al., 2003, 2007; Ma et al., 2006; Castro and Baltieri, 2004; Florez et al., 2008) and nicotine dependence separately (Anthenelli et al., 2008; Campayo et al., 2008; Khazaal et al., 2006).

Our study suggests that topiramate is a useful medication for the treatment of both comorbid alcohol and nicotine misuse. It is important to observe that the decrease of cigarettes smoked during this study, mainly in the topiramate group, occurred even without any specific therapeutic plan for smoking cessation. Due to this, it is tempting to theorize that topiramate has anti-smoking effects as well as the ability to reduce alcohol consumption among alcoholics. In fact, topiramate may antagonize the reinforcing effects related to the release of dopamine by facilitating the actions of

γ -amino-butyric acid (GABA) and antagonizing the excitatory properties of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate glutamate receptors. Besides, due to the ability of topiramate to antagonize L-type calcium channel currents and decrease glutaminergic sensitization, this medication can decrease withdrawal symptoms from alcohol and nicotine. Furthermore, topiramate has demonstrated mild anxiolytic properties, which may reduce the protracted withdrawal symptoms induced by alcohol and nicotine (Johnson, 2004).

Alcoholics quitting smoking without a pharmacological treatment to alleviate withdrawal symptoms from nicotine may have their abilities to deal with the abstinence from alcohol impaired. Diminished capacity to sustain attention and weakened ability to process information, due to the lack of nicotine, can cause difficulties in complying with the medical recommendations and participating in therapeutic activities (Prochaska et al., 2004; Nixon et al., 2007). In fact, alcoholic smokers who try to stop smoking can have lower rates of success with cigarettes cessation than smokers in general (Gulliver et al., 2000). On the other hand, smoking alcoholics who try to stop both substances simultaneously seem to manifest earlier dropout rates than alcoholic non-smokers (Stotts et al., 2003). It is possible that restricting alcohol and tobacco concurrently may lead to poorer treatment outcomes in some patients, unless an adequate pharmacological and psychosocial treatment for both conditions is available.

In fact, research on the effect of smoking cessation on alcohol treatment is somewhat mixed with several studies showing a positive effect and others showing a negative effect. In spite of the mixed findings, it has generally been proposed that treating both is better. However, we must consider that alcoholics, smokers and alcoholic smokers are heterogeneous groups and diverse psychological and clinical factors are associated with increased likelihood of smoking cessation and drinking reduction (Friend and Pagano, 2007). Certainly, there are patients who quit both drugs without pharmacological treatment (Friend and Pagano, 2007); however, others will need a more complex medical management to stop using both drugs. To date, there are no smoking cessation guidelines specifically for alcohol-dependent individuals. Thus, many clinicians have followed medical guidelines for treating tobacco dependence, independently of the treatment of alcoholism. Therefore, the possibility that a pharmacological treatment can be designed to cope with both conditions simultaneously opens up new horizons for patients and doctors.

Our study has not found differences between naltrexone and placebo in the treatment of our patients in terms of smoking reduction, adherence rates and alcohol abstinence rates. In fact, the effects of opiate antagonists, such as naltrexone and naloxone, on smoking cessation have shown mixed results. While some researchers have revealed that these medications may significantly decrease the tobacco use (Covey et al., 1999; Epstein and King, 2004; Ray et al., 2007; Rohsenow et al., 2003), others have not verified this effect on smoking alcoholics or only smokers (King

et al., 2006; Rohsenow et al., 2007; Sutherland et al., 1995). In fact, when naltrexone is associated with nicotine replacement therapy and specific psychosocial management, the outcomes seem to be more promising (Byars et al., 2005; Hutchison et al., 1999; O'Malley et al., 2006). Probably, these controversial results can be partially explained by the heterogeneity of smokers as well. Some authors have reported that naltrexone efficacy on smoking cessation can be influenced by depressive symptoms (Walsh et al., 2008) and even by the gender of the patients (Epstein and King, 2004; King et al., 2006).

The power of the efficacy of topiramate to reduce the number of cigarettes smoked is also shown in this study by the fact that no specific advice was given to the patients on how to stop smoking. Although the decrease in the number of cigarettes smoked can also be an effect of the drinking reduction, there was no significant difference for those who received naltrexone or placebo in terms of number of cigarettes used during this study. Besides, the partial correlations between the quantity of cigarettes smoked and the percentage of abstinence days for each medication prescribed did not show statistical significance. This can mean that there was an independent effect of topiramate on smoking reduction. Actually, other studies have suggested that the abstinence from alcohol among smoking alcoholics can provoke an increase in the number of cigarettes used as a way to circumvent alcohol withdrawal symptoms (Ellingstad et al., 1999; Meyerhoff et al., 2006).

This study has several limitations which need to be further considered:

- (1) Our sample has only included male outpatients. Neurochemical alterations in the brains of males and females are likely to be different, due to the fewer GABA concentrations in female brains (Epperson et al., 2005). In addition, previous studies of naltrexone for smoking cessation suggest that women may be more likely to benefit from naltrexone (Byars et al., 2005; King et al., 2006; Perkins, 2001).
- (2) As this research was not designed specifically to evaluate smoking behavior, some measures that would have better characterized this population with reference to smoking history and outcomes (breath carbon monoxide level or serum cotinine level) were not included in the research plan. Although this can be considered a serious methodological flaw, we have obtained information related to alcohol and tobacco consumption through standardized interviews with these patients and their family members at each appointment.
- (3) We have not applied any psychometric measure to evaluate nicotine-related problems, such as withdrawal symptoms.
- (4) We have merely included cigarette smokers due to the fact that this was the only validated measure of nicotine use that could be obtained using TLFB. Other means of nicotine consumption were not verified.
- (5) Our 12-week trial period was relatively short; thus, longer term testing would be suitable to replicate these findings. Thus, we have not evaluated if the effects of topiramate on the reduction in the number of cigarettes smoked have remained after the 12-week trial period.
- (6) The number of dropouts was high in this study, probably due to the limited structure and psychosocial treatment entailed in the community-based programs where the study was carried out.
- (7) This study has excluded individuals with comorbid axis 1 psychiatric disorders. Therefore, the efficacy of naltrexone in smoking reduction could not be evaluated among depressive alcoholic smokers. As some studies have already demonstrated, naltrexone seems to be useful for these individuals (Covey et al., 1999; Walsh et al., 2008).

In summary, this research has demonstrated that alcoholic smokers can comprise a specific type of alcohol-dependent patient, with higher severity of alcoholism and earlier chance of relapse into drinking. It is tempting to propose that this kind of alcoholic needs more intensive and differential management strategies focusing upon the alcohol consumption. However, as alcoholics consist of a heterogeneous population, it is possible that each smoking alcoholic demonstrates different intentions and beliefs associated with his smoking habits. At least, health professionals should explore the option of dual cessation with their patients and, if possible, provide adequate and effective treatment for both conditions. Topiramate can represent an attractive option for the treatment of alcoholic smokers even if they do not wish to stop both substances at the same time.

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The material has not been published elsewhere. The paper is not currently being considered for publication elsewhere. The authors have been personally and actively involved in substantive work leading to the report, and will hold themselves jointly and individually responsible for its content. All relevant ethical safeguards have been met in relation to subject protection.

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