

The role of alcoholic beverage preference in the severity of alcohol dependence and adherence to the treatment

Danilo Antonio Baltieri*, Fábio R. Daró, Philip L. Ribeiro, Arthur G. De Andrade

Interdisciplinary Group of Studies on Alcohol and Drugs of the Psychiatric Institute of the Clinical Hospitals, Faculty of Medicine, University of São Paulo, Rua Dr Mello Alves, n. 110 Conjunto 01, 01417-010 São Paulo, Brazil

Received 2 July 2008; received in revised form 5 January 2009; accepted 16 January 2009

Abstract

The severity of dependence on alcohol and the efficacy of diverse types of treatments for alcoholism have been the subject of various researches. This study focused on the types of beverages preferentially consumed by alcohol-dependent outpatients and their effects on the severity of dependence and therapeutic outcomes. Our sample comprised 153 patients, 18–60 years of age, with an *International Classification of Diseases* (ICD-10) diagnosis of alcohol dependence, who were randomly divided into three different groups to receive topiramate (up to 300 mg/day), naltrexone (50 mg/day), or placebo during 12 weeks of follow-up. Spirits and beer were the main beverages consumed. At the start of this research, the group of spirits drinkers showed higher severity of alcohol dependence, higher craving for alcohol, more frequent history of treatments for alcoholism, and lower income than the group of beer preference drinkers. During the study, beer preference drinkers demonstrated higher adherence to the treatment, independently of the types of medications prescribed ($P = .02$, odds ratio, 2.46, 95% confidence interval, 1.17–5.19). This study suggests that the severity of dependence and the adherence to the treatment can be factors that set apart beer drinkers from spirits drinkers. As the compliance with the treatment for alcoholism was lower among spirits preference drinkers, a more intensive model of treatment would be necessary. © 2009 Elsevier Inc. All rights reserved.

Keywords: Beverages; Pharmacologic treatments; Alcoholism; Craving

Introduction

Alcoholism comprises one of the major causes of morbidity and mortality worldwide. In Brazil, approximately 11% of the adult population can be considered alcohol dependent (Carlini et al., 2001). Globally, the impact of alcoholism is great in regions with high per-capita consumption, such as Latin America, and seems to be low in regions, such as the Middle East (World Health Organization, 2006). Chronic, recurrent, and excessive alcohol consumption is a well-documented cause of substantial social and health-related burden on society.

Commonly, the rates of compliance with treatment for alcoholism are as low as those for other chronic medical disorders, such as diabetes and hypertension, or even lower (McLellan et al., 2000). Poor treatment adherence can represent reduction of quality of life and loss of life years for many patients (Kripalani et al., 2007). Probably, one of the factors associated with the high rates of treatment

abandonment and relapses during the follow-up is the intensity of craving for alcohol (Flannery et al., 2003). This has been verified when the effectiveness of the association of psychotherapeutic with pharmacologic anti-craving therapy is demonstrated in different trials (Ansoms et al., 2000; De Wildt et al., 2002; Morris et al., 2001; Swift and Pettinati, 2005; Volpicelli, 2001; Weiss and Kueppenbender, 2006).

The high alcohol craving in dependent patients has been related to the volume intake and to the preferential beverage, among other factors (Hillemacher et al., 2006). However, little effort has been made to investigate the relationship between different types of beverages consumed by alcohol-dependent patients and variables associated with outcome measures during the treatment for alcohol dependence, such as adherence to the therapeutic proposals and abstinence rates. On the other hand, studies that focus on different types of alcoholic beverages have more frequently evaluated the influence of types of beverages on the development of diverse physical problems derived from the recurrent alcohol consumption, although a few conclusive statements have been made to date. In fact, different variables, such as socioeconomic status, age, duration of alcohol usage, quantity of ethanol consumed per day,

* Corresponding author. Tel.: +55-11-3082-0649.

E-mail address: dbaltieri@uol.com.br (D.A. Baltieri).

smoking habits, and nutritional status of patients interact in the development of diverse negative consequences for health (Kerr et al., 2000). It is unclear if the choice of different types of beverages, such as beer, wine, or spirits has contributed differently to the adverse effects of heavy alcohol drinking, and scientific research on this subject has shown methodologic flaws (Klatsky et al., 2003). Generally, studies have found that wine drinkers tend to have a healthier lifestyle profile than beer or spirits drinkers, but generally, wine drinkers have shown better socioeconomic levels that can positively influence the health indicators (Becker et al., 2002; Gronbaek et al., 1995; Rimm and Stampfer, 2002; Strandberg et al., 2007). Also, Wilhelm et al. (2008) have pointed out that alcohol dependents who prefer beer to other beverages present less hippocampal damage, in terms of loss of volume, than chronic wine or spirits drinkers. This latter finding has been justified by the lowest homocysteine plasma levels more commonly observed in chronic beer consumers (Bleich et al., 2000; Schlienger, 2003). The vitamins contained in beer, such as B6 vitamin and others of the B complex, seem to be responsible for this reduced level of homocysteine in alcohol dependents who consume this type of beverage (Denke, 2000; Sakuta et al., 2007). Few other studies on beverage choice have focused on the risks of incurring problems, such as drunk driving (Greenfield and Rogers, 1999), violence rates (Norström, 1998), and risk of injuries (Watt et al., 2004). However, with respect to all of these factors, the lifetime amounts of alcohol consumed co-vary with the alcoholic beverage choice, bearing on the results.

Although the preferential consumption of beer has been thought to be associated with higher alcohol craving than the preferential usage of spirits, there are no conclusive studies on the influence of different types of preferential beverages on therapeutic outcomes (Hillemacher et al., 2005). Due to the fact that alcohol-dependent patients commonly show high rates of relapses during treatment, researches on therapeutic managements, pharmacologic trials, and genetic and environmental factors related to the best and the worst therapeutic outcomes, have been continuously carried out. The main aim of these researches has been to improve established medical and psychosocial proposals and develop others to treat this important public health problem.

Typologies for alcoholic patients have also been developed to reduce the heterogeneity among alcoholics and to improve the disposition, assessment, and treatment of this complex population. Generally, these typologies are based on sociodemographic data, personality traces, previous responses to treatments, age onset of alcohol dependence, genetic aspects, and severity of dependence, among others (Chick et al., 2004; Dundon et al., 2004; Hillemacher and Bleich, 2008; Johnson et al., 2006; Kiefer et al., 2008; Saffroy et al., 2008). If the types of alcoholic beverages could affect the response to diverse proposals of treatments

or even craving for alcohol, a new typology might be developed.

Our research has intended to determine whether different preferential beverages consumed by alcohol-dependent outpatients are associated with different therapeutic outcomes and whether certain types of alcoholic beverages are related to higher severity of alcohol dependence and craving at the beginning of the treatment.

Methodology

Participants

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.

This study was part of a pharmacologic trial, where the efficacy of topiramate and naltrexone was compared among alcohol-dependent outpatients, in a randomized, double-blind, placebo-controlled study. One hundred seventy-five 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 other kinds of drug dependence—were assessed to participate in this pharmacologic trial. All selected patients needed to have revealed problems associated with alcohol misuse for at least 2 years. All diagnoses were made by experienced psychiatrists who did not participate in this study.

Patients with serious clinical co-existing diseases (e.g., inadequately controlled diabetes, cardiac failure, and alcoholic cirrhosis), previous treatment with naltrexone or topiramate within 6 months of randomization, any other drug dependence (except nicotine and caffeine), and concomitant psychiatric disorders that might require specific drug treatment were excluded.

Measures

Alcohol intake was documented as volume and percentage of ethanol content of the consumed beverages, so that the alcohol intake in grams (daily intake) could be calculated.

We have separated spirits (cachaça—a strong Brazilian distilled liquor made from sugar cane, vodka, and whisky), beer and wine as types of preferential beverages. The participants were questioned about their current average daily consumption of beer, spirits, and wine, in terms of duration of use and time of drinking (morning, afternoon, or night). Spirits preference drinkers were defined as those who drank more spirits than beer and wine, and vice versa for beer and wine preference drinkers. For a more accurate classification, we defined a particular type of alcoholic beverage as “predominant” if the consumption of that type

of beverage (spirits, beer, or wine) accounted for two-thirds or more of the total amount of ethanol consumed during the last year. This classification system has been used in other researches (Fuchs et al., 2004; Volcik et al., 2008).

In the first interview, after a complete history and clinical examination, patients who fulfilled entry criteria were evaluated. Sociodemographic and personal data, such as daily intake of alcohol in grams, the period of drinking (in years), and the type of alcoholic beverages consumed were obtained in a standardized semi-structured interview, commonly used 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. This questionnaire was administered to the enrolled participants by two specialized doctors, who were trained before the beginning of the study to be able to apply it uniformly.

We also collected self-reported drinking data using a model of the Timeline Followback (TLFB) method (Annis et al., 1996) from weeks 2 to 12, a technique that uses a calendar and memory aids to facilitate retrospective estimates of daily drinking over a specified period. As the patients were assessed eight 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 supervision meeting.

All patients were also evaluated with the Short Alcohol Dependence Data (SADD; Raistrick et al., 1983) at the start of this research, and the Hamilton Depression Rating Scale (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 was evaluated on the basis of each patient's self-report and by interviewing a family member whenever he or she was available. Alcohol abuse hepatic indexes, such as γ -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.

Procedure

Subjects were informed about the study objectives, the nature of the treatment provided, the profile of medications tested, and that the medications they would receive would be chosen at random.

The methodology of this randomized, double-blind, placebo-controlled study has been previously described (Baltieri et al., 2008). In brief, patients screened for this research were randomly divided into three groups (placebo, naltrexone, and topiramate). All patients received two identical capsules a day for 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 progressively higher quantities of topiramate tablets (25, 50, or 100 mg) in each week, because the dose of topiramate had to reach 300 mg/day by week 8. In this group, from week 8 to the end of week 12, the dose of

Table 1
Topiramate dose-escalating schedule

Weeks	Morning capsule (g)	Night capsule (g)	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

topiramate remained at 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 were identical for the three groups. The returned packages at each supervision meeting as well as 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 program if they relapsed or failed to comply with the medication and that they could choose to leave the program at any time.

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

Brief cognitive behavioral therapy

All patients were submitted to standardized brief cognitive behavioral interventions by their doctors. The general goal of the therapy was to improve the person's ability to manage high-risk situations that could precipitate relapse. At each supervision meeting, the doctors evaluated the drinking behavior of the patients and used motivational interviewing strategies. Management of negative mood, assertiveness, drink refusal skills, enhancement of social support networks, and relapse prevention were standardized and applied to each patient during this treatment.

Outcome measures

We verified dissimilarities among the different types of preferential drinkers in terms of craving, depressive symptoms, and alcohol abuse hepatic indexes at the start and the end of this study.

We also verified differences among the types of preferential drinkers in terms of drinking behavior during the treatment, after adjustment for the different medications used. With respect to this, the main outcome criteria were:

- (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 of ethanol);
- (2) *Cumulative abstinence duration*: 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) *Compliance with the treatment*: we have considered three reasons for dropping out of the research, such as “refusal to continue” (the patient affirmed that he wanted to stop this type of treatment and to try others, e.g., psychotherapy only); “protocol violation” (the patient used other psychopharmacologic 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). The patients who remained in the treatment during all 12 weeks were considered adherent. Patients who did not attend follow-up and whose outcome was unknown were considered to have dropped out of the trial.

Statistical analysis

Group definition

As only two patients were wine preference drinkers, we discharged this group and only compared beer preference drinkers with spirits preference drinkers, because one group with only two subjects would harm the statistical analysis. In Brazil, the rates of spirits consumption (specially “cachaça”) are higher than those of wine consumption among people of low socioeconomic status (Brasil, 2007) and this may have been reflected in our sample. Besides, wine drinkers seem to have better socioeconomic status than spirits and beer drinkers (Rimm and Stampfer, 2002) and our research was carried out in a public hospital, where most patients have low socioeconomic levels. Furthermore, our sample included only males, due to the fact that our service is specific for the treatment of alcohol-dependent males.

Baseline differences

Baseline differences between these two groups (beer and spirits preference drinkers) were determined using the parametric *t* test for continuous variables, except when the variances between two variables of the samples were unequal, according to Levene’s criteria. In these situations, we used the nonparametric Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test. A multiple analysis of variance (MANOVA) was also applied because this research evaluated many dependent variables and using only univariate analyses could increase the chance of missing data. Logistic regression analysis was also constructed to

investigate the associations between the two types of drinkers, according to the preferential beverages, and the variables related to severity of alcohol dependence, after adjustment for others that could possibly confound this relation.

Drinking behavior during the study

Statistical analysis of the main efficacy criteria followed the intention-to-treat 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 supervision meeting or withdrew from the study were deemed to be nonabstinent at the time those data were not available.

Time to first relapse and cumulative abstinence duration were analyzed using the parametric *t* test, except when the variances between two variables of the samples were unequal, according to the Levene’s criteria. In these situations, the nonparametric Mann–Whitney *U* test could be used.

As the beer preference drinkers and the spirits preference drinkers were treated with different medications, we used the *Cox Proportional Hazards Regression Analysis* for the adjustment of two independent variables or covariates (different types of drinkers, according to the preferential beverages, and different types of medications used) that 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.

A multiple analysis of co-variance (MANCOVA) was also used, because this research evaluated many dependent variables, and it was essential to adjust the dependent variables’ scores for pretreatment differences. As all subjects were tested for depression and craving at the start and at the end of this research, and for the severity of alcohol dependence only at the start of this study, we combined these two dependent variables (which were measured at the end of this research) and adjusted them for differences in three covariates (the variables that were obtained at the start of this study—total mean scores of the Hamilton Depression Rating Scale, the OCDS, and the SADD).

In addition, alcohol abuse hepatic indexes (GGT, AST, ALT, and MCV) were measured at the start and at the end of this research. To avoid the probability of missing data and to adjust the dependent variables for the covariates, we also used a MANCOVA. The hepatic indexes verified at the end of this research (dependent variables) were combined and adjusted for differences in the covariates (hepatic indexes verified at the start of this study).

For all statistical tests performed, differences between both groups were accepted as significant if they achieved the .05 level with two-tailed tests. Data were analyzed using the SPSS 14 (SPSS Inc., Chicago, IL) and Stata 9 statistical packages.

Results

Sample characteristics

Of the 175 screened patients, 14 (8.00%) refused to participate in this study, and 6 (3.43%) were excluded because they presented with co-existing diseases that could harm their adequate participation.

Two patients (1.14%) revealed that they preferentially consumed wine. Because of this small number of wine preference drinkers in our sample, we preferred to exclude them from our statistical analysis.

Of the 153 selected patients, 106 (69.30%) were spirits preference drinkers and 47 (30.70%) were beer preference drinkers. There were no significant differences between these groups in terms of types of medications prescribed and sociodemographic aspects. However, the beer drinkers showed higher monthly income than the spirits drinkers (Mann–Whitney $U = 1833$, $P < .01$; Table 2).

Also, there were no significant differences between both groups with respect to the following variables: years since alcohol-related problems occurred, mean number of

cigarettes smoked per day, and quantity of ethanol consumed per day (in grams) (Table 2).

Beer preference drinkers showed lower AST serum levels than the group of spirits preference drinkers ($t = 2.14$, 151 degree of freedom [df], $P = .04$). Also, the group of beer drinkers demonstrated lower MCV serum levels than the spirits preference drinkers ($t = 2.56$, 151 df, $P = .01$) at the start of the treatment. There were no significant differences between both groups with reference to the GGT and ALT serum levels (Table 2).

Baseline psychometric measures

A 2×3 MANOVA was conducted, with the groups of preferential drinkers (beer and spirits) as the independent variable, and the SADD, the OCDS and the Hamilton Depression Rating Scale total mean scores obtained at the start of this study as the dependent variables. The overall MANOVA was significant, Pillai's $F(3, 148) = 5.45$, $P < .01$, $\partial n^2 = 0.09$. Univariate analyses revealed significant effects for the SADD total mean score ($t = 3.72$, 151

Table 2
Baseline characteristics

Variables	Spirits drinkers ($n = 106$)	Beer drinkers ($n = 47$)	P value
Age, mean (S.D.)	44.07 (8.06)	44.75 (9.31)	$t = 0.46$, 151 df, $P = .65$
Race, n (%)			
White	72 (67.92)	36 (76.59)	$\chi^2 = 1.45$, 2 df, $P = .48$
Black	9 (8.49)	2 (4.26)	
Mulatto	25 (23.59)	9 (19.15)	
Marital status, n (%)			
Married	51 (48.11)	27 (57.45)	$\chi^2 = 1.37$, 2 df, $P = .50$
Single	20 (18.87)	6 (12.77)	
Separated/Widowed	35 (33.02)	14 (29.78)	
Education, n (%)			
Sixth grade or less	29 (27.36)	9 (19.15)	$\chi^2 = 1.63$, 3 df, $P = .65$
7th–12th grade	30 (28.30)	13 (27.66)	
High School graduate	36 (33.96)	18 (38.30)	
Unfinished/completed college	11 (10.38)	7 (14.89)	
Quantity of ethanol per day (g), ^a mean (S.D.)	319.49 (175.61)	260.49 (167.84)	$t = 1.94$, 151 df, $P = .06$
Years since alcohol-related problems occurred, mean (S.D.)	36.64 (8.33)	34.53 (9.83)	$t = 0.07$, 151 df, $P = .94$
Cigarettes per day, mean (S.D.)	17.57 (11.94)	15.00 (12.55)	$t = 1.23$, 151 df, $P = .23$
Family history positive for alcoholism, n (%)	83 (78.30)	41 (87.23)	$\chi^2 = 1.69$, 1 df, $P = .19$
Previous treatment for alcoholism, n (%)	62 (58.49)	19 (40.43)	$\chi^2 = 4.26$, 1 df, $P = .04^*$
Monthly income (In R\$, the Brazilian currency), mean (S.D.)	708.25 (732.34)	1148.38 (1074.72)	$U = 1833$, $P < .01^{**}$
Randomized treatment, n (%)			
Naltrexone	35 (33.02)	14 (29.79)	$\chi^2 = 0.20$, 2 df, $P = .90$
Topiramate	36 (33.96)	16 (34.04)	
Placebo	35 (33.02)	17 (36.17)	
Plasma GGT, U/L; (reference range 8–61), mean (S.D.)	105.27 (116.22)	109.94 (111.12)	$t = 0.23$, 151 df, $P = .82$
Plasma AST, U/L; (reference range < 37) mean (S.D.)	46.09 (39.21)	32.89 (20.15)	$t = 2.14$, 151 df, $P = .04^*$
Plasma ALT, U/L; (reference range < 41) mean (S.D.)	37.95 (26.91)	34.29 (22.16)	$t = 0.80$, 151 df, $P = .42$
Plasma MCV, f/L; (reference range 80–100) mean (S.D.)	96.16 (6.77)	93.07 (6.72)	$t = 2.56$, 151 df, $P = .01^*$

Abbreviations: GGT = γ -glutamyl transferase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MCV = mean cellular volume; S.D. = standard deviation; df = degree of freedom.

* $P < .05$.

** $P < .01$.

^aAlcohol usage during the last 3 months preceding the first day of the study.

Table 3
Baseline psychometric measures

Variables	Spirits drinkers (n = 106)	Beer drinkers (n = 47)	P value
SADD, mean (S.D.)	30.64 (8.26)	25.32 (7.93)	$t = 3.72$, 151 df, $P < .01^{**}$
OCDS, mean (S.D.)	51.47 (12.99)	46.00 (13.17)	$t = 2.39$, 151 df, $P = .02^*$
Hamilton, mean (S.D.)	10.96 (6.96)	9.57 (7.05)	$t = 1.13$, 151 df, $P = .26$

Abbreviations: SADD = Short Alcohol Dependence Data; OCDS = Obsessive Compulsive Drinking Scale; S.D. = standard deviation; df = degree of freedom.

* $P < .05$.

** $P < .01$.

df, $P < .01$), and for the OCDS total mean score ($t = 2.39$, 151 df, $P = .02$). There was no significant difference between both groups in the analysis of univariate effects for Hamilton Depression Rating Scale (Table 3).

Severity of alcoholism after adjustment for confounders

As the spirits preference drinkers frequently more reported previous treatment for alcoholism scored higher in the SADD and OCDS inventories and revealed lower monthly income than beer preference drinkers, we decided to verify the association of the severity of alcohol dependence with the types of drinkers, after adjustment for the other variables. Also, as the correlation between SADD and OCDS was significantly positive (Pearson = 0.72, $P < .01$), only SADD was entered into the analysis to avoid that one of these variables suppressed the effect of the other. In fact, as we chose to apply the model of direct logistic regression, where all predictors enter the equation simultaneously (as long as tolerance is not violated), a predictor that is highly correlated with the outcome by itself may show little predictive capability in the presence of other highly correlated predictors. Another study revealed a high positive correlation between OCDS and other instruments for measuring severity of alcohol dependence (Moak et al., 1998).

Direct logistic regression was performed on group status (beer preference drinkers and spirits preference drinkers) as outcome and three predictors: SADD total mean scores, history of treatment for alcoholism, and income. These variables were chosen because they showed statistical

significance in univariate analyses and could confound their association with the types of drinkers. A test of the full model with all predictors against a constant-only model was statistically reliable, $\chi^2 = 23.37$, 3 df, $P < .01$. The variance in group membership accounted for was marginal, with Nagelkerke $R^2 = 0.20$. Prediction success was impressive for the group of spirits preference drinkers, with 91.5% of these patients being correctly classified. Prediction was far less impressive for the beer preference drinkers, with 38.3% being correctly classified. The overall success rate for prediction was 75.20%. According to the Wald criterion, the three variables reliably predicted group membership (Wald = 21.54, 1 df, $P < .01$, odds ratio (OR), 2.26). In fact, higher mean score in SADD (or higher mean score in OCDS at the start of the treatment), lower monthly income, and more frequent history of treatment reliably predicted the group of spirits preference drinkers (Table 4).

Outcome measures (intention to treat)

Alcohol abuse hepatic indices

A $2 \times 4 \times 4$ MANCOVA was performed, with the types of drinkers (beer and spirits) as the independent variable, GGT, ALT, AST, and MCV total mean levels at the end of this study as the dependent variables, and GGT, ALT, AST, and MCV total mean levels assessed at the start of this study as covariates. The overall MANCOVA was not significant, Pillai's $F(4, 74) = 0.98$, $P = .42$, $\partial n^2 = 0.05$.

A univariate analysis demonstrated that beer preference drinkers showed lower MVC total mean score than spirits drinkers at the end of the study ($t = 2.55$, 81 df, $P = .01$). As this variable measured at the beginning of the study also revealed statistical significance when both groups of drinkers were compared, we conducted an analysis of covariance (ANCOVA), with the MVC total mean score obtained at the start of the study as covariate. In this analysis, there was no significant difference between both groups ($F = 0.03$, 1 df, $P = .85$). Therefore, there was no significant difference between beer and spirits preference drinkers with reference to the MVC serum levels at the end of this study, after removing the effects of the MVC levels evaluated at the start of this research.

Analyses of univariate effects did not reveal significant effects for GGT, AST, and ALT at the end of this study (Table 5).

Table 4
Effects of alcoholism-related variables on spirits preference drinkers at the beginning of the treatment (direct logistic regression)

Variables	S.E.	Wald	df	P	OR	95% CI
Constant	0.71	2.35	1	.12	0.34	—
SADD mean scores	0.02	9.42	1	<.01**	1.07	1.03–1.13
Previous treatment for alcoholism	0.38	4.10	1	.04*	2.18	1.02–4.62
Income	<0.01	6.17	1	.01*	0.99	0.99–1.00

Abbreviations: SADD = Short Alcohol Dependence Data; OR = odds ratio; S.E. = standard error of mean; CI = confidence interval.

* $P < .05$.

** $P < .01$.

Table 5
Drinking outcome variables at the end of the study between beer preference drinkers and spirits preference drinkers (intention to treat)

Variables	Spirits drinkers	Beer drinkers	P value
Time to first relapse (in weeks), mean (S.D.)			
Naltrexone group	5.48 (4.56)	6.15 (5.38)	$t = 0.43, 47 \text{ df}, P = .67$
Topiramate group	7.22 (4.98)	8.86 (4.67)	$t = 0.95, 50 \text{ df}, P = .34$
Placebo group	4.43 (4.55)	5.65 (5.29)	$t = 0.86, 50 \text{ df}, P = .39$
Total (involving all groups)	5.73 (4.80)	6.81 (5.18)	$t = 1.25, 151 \text{ df}, P = .21$
Cumulative abstinence duration (in weeks), mean (S.D.)			
Naltrexone group	6.11 (4.64)	7.86 (5.32)	$t = 1.14, 47 \text{ df}, P = .26$
Topiramate group	7.61 (4.71)	9.37 (3.99)	$t = 1.30, 50 \text{ df}, P = .19$
Placebo group	5.00 (4.58)	6.41 (5.33)	$t = 0.99, 50 \text{ df}, P = .33$
Total (involving all groups)	6.25 (4.72)	7.85 (4.96)	$t = 1.89, 151 \text{ df}, P = .06$
OCDS, mean (S.D.)	22.65 (8.90)	21.25 (9.67)	$t = 0.67, 81 \text{ df}, P = .50$
Hamilton Depression Rating Scale, mean (S.D.)	5.47 (4.35)	4.87 (4.31)	$t = 0.61, 81 \text{ df}, P = .54$
Plasma GGT, U/L; (reference range 8–61), mean (S.D.)	74.13 (101.57)	72.53 (89.87)	$t = 0.93, 81 \text{ df}, P = .93$
Plasma AST, U/L; (reference range < 37), mean (S.D.)	24.67 (12.43)	21.47 (8.93)	$t = 1.26, 81 \text{ df}, P = .21$
Plasma ALT, U/L; (reference range < 41), mean (S.D.)	23.71 (19.96)	23.03 (16.72)	$t = 0.16, 81 \text{ df}, P = .87$
Plasma MCV, f/L; (reference range 80–100), mean (S.D.)	92.86 (3.67)	89.88 (6.94)	$t = 2.55, 81 \text{ df}, P = .01^*$
Adherence to the treatment, n (%)	51 (48.11)	32 (68.08)	$\chi^2 = 5.23, 1 \text{ df}, P = .02^*$
Participation in Alcoholics Anonymous Groups, n (%)	9 (8.49)	7 (14.89)	$\chi^2 = 1.43, 1 \text{ df}, P = .23$
Reasons for discontinuation of the study, n (%)			
Refusal to continue	7 (6.60)	2 (4.26)	$\chi^2 = 0.02, 2 \text{ df}, P = .99$
Follow-up dropout	40 (37.74)	11 (23.40)	
Protocol violation	8 (7.55)	2 (4.26)	

Abbreviations: OCDS = Obsessive Compulsive Drinking Scale; GGT = γ -glutamyl transferase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MCV = mean cellular volume; S.D. = standard deviation; df = degree of freedom.

* $P < .05$.

Efficacy variables of the treatment

There were no significant differences between both groups with relation to the time to first relapse and cumulative abstinence duration, independently of the types of medications prescribed. At the end of this study, beer and spirits preference drinkers did not show significant differences in the OCDS and the Hamilton Depression Rating Scale total mean scores. Besides, there was no significant difference between both groups with reference to the voluntary participation in Alcoholics Anonymous Groups (Table 5).

We also used the *Cox Proportional Hazards Regression Model* to control the effects of both variables—“types of drinkers” and “types of medications prescribed”—at the time to first relapse. According to the Wald criterion, the preferential consumption of beer did not reliably predict survival time, after adjustment for the different medications used (Wald = 1.67, 1 df, $P = .19$, OR, 0.75, 95% confidence interval [CI], 0.48–1.16). However, according to the same criterion, the use of topiramate reliably predicted survival time, after adjustment for the types of drinkers and for the other medications prescribed (Wald = 4.31, 1 df, $P = .04$, OR, 0.60, 95% CI, 0.37–0.97). In this analysis, the OR of 0.60 means that the use of topiramate decreases the odds of failing by 40%. The use of naltrexone and placebo did not predict survival time, after adjustment for the other variables (use of topiramate and types of drinkers). The analysis involving the efficacy of these three drugs has been described elsewhere.

Adherence to the treatment

Fifty-one (48.11%) spirits preference drinkers and 32 (68.08%) beer preference drinkers adhered to this treatment ($\chi^2 = 5.23, 1 \text{ df}, P = .02$).

As the groups of patients who preferred to drink either beer or spirits received different medications during the treatment (topiramate, naltrexone, and placebo), we carried out a logistic regression to adjust the effects of the types of medications prescribed and of the types of preferential beverages, which could confound the prediction about the outcome.

Considering the adherence to the treatment as outcome and the variables “types of drinkers” and “types of medications prescribed” as predictors, a stepwise logistic regression was conducted. We chose this method (stepwise) because both predictors might be highly correlated with the outcome (adherence to the treatment) and one could bump out the effect of the other.

In Step 1, where only the predictor “types of drinkers” was included, the model was statistically reliable, ($\chi^2 = 5.34, 1 \text{ df}, P = .02$). The variance in group membership accounted for was very low, with Nagelkerke $R^2 = 0.05$. Prediction success was high for the patients who did not adhere to the treatment, with 78.6% being correctly classified. Prediction was less impressive for the patients who adhered to the treatment, with 38.6% being correctly classified. The overall success rate for prediction was 56.9%. According to the Wald criterion, the group of

Table 6
Effects of the types of drinkers and of the types of medications prescribed on the adherence to the treatment (stepwise logistic regression)

Variables	S.E.	Wald	df	P	OR	95% CI
Step 1						
Constant	0.19	0.15	1	.69	0.93	—
Beer preference drinkers	0.37	5.12	1	.02*	2.30	1.12–4.74
Step 2						
Constant	0.32	4.80	1	.03*	0.50	—
Beer preference drinkers	0.38	5.64	1	.02*	2.46	1.17–5.19
Treatment	—	6.68	2	.03*	—	—
Treatment with naltrexone	0.42	3.99	1	.046*	2.29	1.02–5.19
Treatment with topiramate	0.41	5.83	1	.02*	2.72	1.21–6.12

Abbreviations: S.E. = standard error of the mean; CI = confidence interval; OR = odds ratio; df = degree of freedom.

* $P < .05$.

beer preference drinkers reliably predicted the adherence to the treatment (Wald = 5.12, 1 df, $P = .02$, OR, 2.30, 95% CI, 1.12–4.74) (Table 6).

In Step 2, where the predictors “types of drinkers” and “types of medications used” were included, the model was also statistically reliable, ($\chi^2 = 12.23$, 3 df, $P < .01$). The variance in group membership accounted for was better than that in step one, with Nagelkerke $R^2 = 0.11$. Prediction success was high for the patients who adhered to the treatment, with 85.5% being correctly classified. Prediction was much lower for the patients who did not adhere to the treatment, with 32.9% being correctly classified. The overall success rate for prediction was 61.4%. In this step, the variable “beer preference drinkers” also predicted the outcome “adherence to the treatment” reliably, according to the Wald criterion (Wald = 5.64, 1 df, $P = .02$, OR, 2.46, 95% CI, 1.17–5.19) (Table 6).

Discussion

This study showed that spirits preference drinkers demonstrated higher severity of alcohol dependence and craving for alcohol, more frequent history of treatments for alcoholism, lower monthly income, and higher AST and MCV serum levels than the beer preference drinkers at the start of the study. The spirits preference drinkers have also demonstrated lower adherence to the treatment, independently of the types of medications prescribed.

Some studies have indicated a beverage-dependent influence on craving. In fact, the influence of different types of beverages on the severity of alcohol dependence and craving can be an epiphenomenon of confounding variables, such as cultural or socioeconomic factors (Hillemacher et al., 2005; Jensen et al., 2002). Contrary to the findings of other researches that have verified higher

craving among beer preference drinkers than spirits or wine preference drinkers, more probably due to the greater volume intake of beer than other beverages (Geerlings and Lesch, 1999; Hillemacher et al., 2005), our study demonstrated that beer drinkers revealed lower severity of alcohol dependence and craving, and higher compliance with the treatment proposed than spirits drinkers. In fact, alcohol craving is thought to appear either from the desire to have alcohol’s positive effects (i.e., positive reinforcement) or from the desire to circumvent the negative effects of withdrawal symptoms (i.e., negative reinforcement), but further models have also proposed other important dimensions of craving, such as the desire and intention to consume alcohol, lack of control over alcohol use, and preoccupation with drinking-related thoughts and/or behavior. Therefore, certain aspects of craving can better characterize the experience of some alcoholics than that of others, what can render the evaluation of craving much more complex (Drobes and Thomas, 1999; Sinha and O’Malley, 1999).

As different models of cravings have been observed among alcoholics and related to various neurobiological processes, researchers and clinicians have dedicated considerable efforts to understand what kind of pharmacologic treatment might be most efficacious at improving a particular type of craving (Johnson et al., 2006). Also, it is tempting to suppose that different types of beverages preferentially consumed can interfere in these processes differently. Published research on the connection between types of preferential beverages and intensity and characteristics of alcohol craving has been scant and the cultural influences on this relationship have not been adequately investigated.

Many studies have pointed out diverse neurobiological mechanisms involved with craving for alcohol, mainly those related to reactivation of the reward neurotransmitters systems, such as γ -aminobutyric acid, glutamate, opioid peptides, dopamine, and serotonin (Goldstein and Volkow, 2002; Hillemacher et al., 2004; Johnson et al., 2006). More recently, other researches have also shown that neuroendocrinologic mechanisms, including changes of the hypothalamus–pituitary–adrenocortical axis, seem to be of special importance in groups of alcoholics (Hillemacher and Bleich, 2008; Kiefer et al., 2002). Among different endocrinological systems, some appetite-regulating peptides have been implicated in the craving for alcohol, such as leptin, ghrelin, and adiponectin (Addolorato et al., 2006; Hillemacher et al., 2007, 2009). According to Hillemacher et al. (2007), leptin serum levels are positively related to the magnitude of alcohol craving among male and female alcoholics. Besides, the impact of leptin serum levels on alcohol craving seems to be higher among beer drinkers than spirits drinkers. Other studies have focused on the influence of total volume intake of alcoholic beverages on craving. In fact, changes in volume-regulating peptides, such as vasopressin and atrial natriuretic peptide have been

associated with alcohol craving as well (Döring et al., 2003; Hillemacher and Bleich, 2008). In general, the total volume intake of beer drinkers is higher than that of spirits or wine drinkers. Despite these findings, alcohol craving is also associated with the daily consumed amount of ethanol, and spirits drinkers may be using higher quantities of ethanol than beer drinkers. Our research has demonstrated that spirits drinkers have consumed almost 1.23 times more ethanol than beer drinkers, although this difference has not been statistically significant. Besides, the high severity of alcohol dependence (Yoon et al., 2006), and the precocious beginning of alcohol problems (Johnson et al., 2000) have been significantly associated with craving. Our study has shown that spirits drinkers have demonstrated higher severity of alcohol dependence and earlier beginning of alcohol problems than beer drinkers.

However, alcohol-dependent patients consist of a heterogeneous population and diverse variables must be taken into account during medical and psychological evaluations. Cultural and social factors, such as availability and low price of certain beverages, low socioeconomic status and limited repertoire of social and family activities of drinkers should be considered adequately.

Our sample comprised mainly spirits drinkers, despite the fact that beer is the most consumed beverage in our country (Brasil, 2007). Certainly, beer is more heavily marketed than spirits and is peddled by the media (e.g., on network television). Researches indicate that there is more marketing exposure for beer than for other beverages, which can convince people that this type of alcoholic beverage is less harmful than others (Greenfield and Rogers, 1999; Naimi et al., 2007). This may delay the search for an adequate treatment by excessive beer consumers. Although there was no significant difference between both groups of drinkers in terms of age at the beginning of the study, the group of spirits drinkers more frequently looked for other therapeutic services before starting our research. This suggests that alcohol-dependent patients who prefer spirits to beer can have an earlier perception of health problems induced by this type of beverage. One study by Gronbaek et al. (1999) demonstrated a slightly more negative self-perception of the physical health among spirits drinkers than beer drinkers.

Some studies have reported higher incidence of severe liver damage among spirits drinkers than beer and wine preference drinkers (Gronbaek et al., 2004; Kerr et al., 2000). In fact, many factors can be associated with this connection, such as poorer nutritional status linked to lower income, larger quantities of ethanol per occasion, and more persistent daily drinking, among others. Our research also revealed that spirits drinkers reported lower monthly income than beer drinkers, although there were no significant differences in other sociodemographic data. Low income is commonly related to inadequate nutritional quality.

Spirits, such as cachaça, can contain high levels of higher alcohols, mainly in illicit or home-produced beverages. This

can mean that there may be further carcinogenic or liver-toxic contaminants in these alcoholic beverages and that the possibility of synergistic effects between ethanol and such other contaminants exists (Lachenmeier et al., 2008). Our study has shown that spirits preference drinkers presented higher MVC and AST serum levels at the start of the study, what can be related to the high severity of alcohol dependence as well as to the type of beverage consumed.

The higher the severity of a certain disease, the higher the therapeutic attempts provided to patients must be. Our study suggests that spirits preference drinkers should receive higher efforts during their management, due to the fact that the compliance with the treatment tends to be lower and that the severity of alcohol dependence is higher at the beginning of the treatment among these types of drinkers, as our study demonstrated.

The creation of typologies is a complex task, because multiple genetic, sociodemographic, environmental, and personality-related factors are involved. Although our study revealed that spirits preference drinkers present a more severe dependence on alcohol and a lower adherence to the treatment, these patients have low financial resources, and many of them are unemployed. In our country, it is cheaper to take high doses of “cachaça” (the most common spirits consumed by our subjects) than high quantities of beer. Also, a longer history of therapeutic failures can discourage patients from adhering to a new proposal of management. Unfortunately, many people search for, and readily accept impressions that support their previous beliefs, behaviors, and goals, and they frequently ignore contrary evidences (Harris, 1991). The medical professionals have to cope with these misconceptions or cognitive distortions revealed by their patients, aiming to improve the therapeutic results.

To our knowledge, our study is the first pharmacologic trial to treat alcohol-dependent outpatients in which an analysis by type of beverage consumed has also been performed.

There were, however, some weaknesses in this study:

- (1) Our sample included only men and did involve wine preference drinkers. In fact, the rates of consumption of spirits (specially cachaça) were higher than that of wine among males of low socioeconomic status in our country;
- (2) This study involved only males, and a comparison with females would be particularly interesting;
- (3) This research primarily focused on the therapeutic efficacy of topiramate, naltrexone, and placebo for alcohol-dependent outpatients. Other therapeutic proposals were not tested;
- (4) The number of dropouts was high in this study, probably as a result of its design, which allowed patients to follow the standard community-based programs of treatment, without norms to increase patient retention;
- (5) A larger sample size could provide higher power for our comparison, besides including wine preference drinkers.

Acknowledgments

This study was supported by grants from FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo—The State of São Paulo Research Foundation). The authors wish to thank CISA (Centro de Informações sobre Saúde e Álcool—Center for Information on Health and Alcohol) and the Pharmacy Sector at the Psychiatric Institute of the Clinical Hospital of the University of São Paulo, Brazil.

References

- Addolorato, G., Capristo, E., Leggio, L., Ferrulli, A., Abenavoli, L., Malandrino, N., et al. (2006). Relationship between ghrelin levels, alcohol craving, and nutritional status in current alcoholic patients. *Alcohol Clin. Exp. Res.* *30*, 1933–1937.
- Annis, H. M., Sobell, L. C., Ayala-Velazquez, H., Rybakowski, J. K., Sandahl, C., Saunders, B., et al. (1996). Drinking-related assessment instruments: cross-cultural studies. *Subst. Use Misuse* *31*, 1525–1546.
- Ansoms, C., Deckers, F., Leher, P., Pelc, I., and Potgieter, A. (2000). An open study with acamprosate in Belgium and Luxemburg: results on sociodemographics, supportive treatment and outcome. *Eur. Addict. Res.* *6*, 132–140.
- Anton, R. F., Moak, D. H., and Latham, P. (1995). The Obsessive Compulsive Drinking Scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. *Alcohol Clin. Exp. Res.* *19*, 92–99.
- Baltieri, D. A., Daro, F. R., Ribeiro, P. L., and De Andrade, A. G. (2008). Comparing topiramate with naltrexone in the treatment of alcohol dependence. *Addiction* *103*, 2035–2044.
- Becker, U., Gronbaek, M., Johansen, D., and Sorensen, T. I. (2002). Lower risk for alcohol-induced cirrhosis in wine drinkers. *Hepatology* *35*, 868–875.
- Bleich, S., Degner, D., Javaheripour, K., Kurth, C., and Kornhuber, J. (2000). Homocysteine and alcoholism. *J. Neural. Transm.* *60*, S187–196.
- Brasil. Presidência da República (2007). *I Levantamento Nacional sobre os Padrões de Consumo de Álcool na População Brasileira*. Brasília: Secretaria Nacional Anti-Drogas.
- Carlini, E. A., Galduroz, J. C. F., Notto, A. R., & Nappo, S. A. (Eds.). (2001). *Levantamento domiciliar de drogas psicotrópicas no Brasil: estudo envolvendo as 107 maiores cidades do país*. São Paulo: CEBRID/UNIFESP.
- Chick, J., Aschauer, H., and Hornik, K. (2004). Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology. *Drug Alcohol Depend.* *74*, 61–70.
- Denke, M. A. (2000). Nutritional and health benefits of beer. *Am. J. Med. Sci.* *320*, 320–326.
- De Wildt, W. A., Schippers, G. M., Van Den Brink, W., Potgieter, A. S., Deckers, F., and Bets, D. (2002). Does psychosocial treatment enhance the efficacy of acamprosate in patients with alcohol problems? *Alcohol Alcohol.* *37*, 375–382.
- Döring, W. K., Herzenstiel, M. N., Krampe, H., Jahn, H., Pralle, L., Sieg, S., et al. (2003). Persistent alterations of vasopressin and N-terminal proatrial natriuretic peptide plasma levels in long-term abstinent alcoholics. *Alcohol Clin. Exp. Res.* *27*, 849–861.
- Drobos, D. J., and Thomas, S. E. (1999). Assessing craving for alcohol. *Alcohol Res. Health* *23*, 179–186.
- Dundon, W., Lynch, K. G., Pettinati, H. M., and Lipkin, C. (2004). Treatment outcomes in type A and B alcohol dependence 6 months after serotonergic pharmacotherapy. *Alcohol Clin. Exp. Res.* *28*, 1065–1073.
- Flannery, B. A., Poole, S. A., Gallop, R. J., and Volpicelli, J. R. (2003). Alcohol craving predicts drinking during treatment: an analysis of three assessment instruments. *J. Stud. Alcohol* *64*, 120–126.
- Fuchs, F. D., Chambless, L. E., Folsom, A. R., Eigenbrodt, M. L., Duncan, B. B., Gilbert, A., et al. (2004). Association between alcoholic beverage consumption and incidence of coronary heart disease in whites and blacks: the Atherosclerosis Risk in Communities Study. *Am. J. Epidemiol.* *160*, 466–474.
- Geerlings, P., and Lesch, O. M. (1999). Introduction: craving and relapse in alcoholism: neurobio-psychosocial understanding. *Alcohol Alcohol.* *34*, 195–196.
- Goldstein, R. Z., and Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am. J. Psychiatry* *159*, 1642–1652.
- Greenfield, T. K., and Rogers, J. D. (1999). Alcoholic beverage choice, risk perception and self-reported drunk driving: effects of measurement on risk analysis. *Addiction* *94*, 1735–1743.
- Gronbaek, M., Deis, A., Sorensen, T. I., Becker, U., Schnohr, P., and Jensen, G. (1995). Mortality associated with moderate intakes of wine, beer, or spirits. *BMJ* *310*, 1165–1169.
- Gronbaek, M., Jensen, M. K., Johansen, D., Sorensen, T. I., and Becker, U. (2004). Intake of beer, wine and spirits and risk of heavy drinking and alcoholic cirrhosis. *Biol. Res.* *37*, 195–200.
- Gronbaek, M., Mortensen, E. L., Mygind, K., Andersen, A. T., Becker, U., Gluud, C., et al. (1999). Beer, wine, spirits and subjective health. *J. Epidemiol. Community Health* *53*, 721–724.
- Harris, M. J. (1991). Controversy and culmination: meta-analysis and research on interpersonal expectancy effects. *Pers. Soc. Psychol. Bull.* *17*, 316–322.
- Hamilton, M. (1960). A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* *23*, 56–62.
- Hillemacher, T., Bayerlein, K., Reulbach, U., Sperling, W., Wilhelm, J., Mugele, B., et al. (2005). Influence of beer, wine and spirits consumption on craving. *Addict. Biol.* *10*, 181–186.
- Hillemacher, T., Bayerlein, K., Wilhelm, J., Poleo, D., Frieling, H., Ziegenbein, M., et al. (2006). Volume intake and craving in alcohol withdrawal. *Alcohol Alcohol.* *41*, 61–65.
- Hillemacher, T., Bleich, S., Frieling, H., Schanze, A., Wilhelm, J., Sperling, W., et al. (2007). Evidence of an association of leptin serum levels and craving in alcohol dependence. *Psychoneuroendocrinology* *32*, 87–90.
- Hillemacher, T., and Bleich, S. (2008). Neurobiology and treatment in alcoholism—recent findings regarding Lesch's typology of alcohol dependence. *Alcohol Alcohol.* *43*, 341–346.
- Hillemacher, T., Reulbach, U., Bayerlein, K., Wilhelm, J., Bonsch, D., Sperling, W., et al. (2004). Plasma homocysteine concentrations do not influence craving in alcohol withdrawal. *Alcohol* *34*, 211–215.
- Hillemacher, T., Weinland, C., Heberlein, A., Groschl, M., Schanze, A., Frieling, H., et al. (2009). Increased levels of adiponectin and resistin in alcohol dependence—possible link to craving. *Drug Alcohol Depend.* *99*, 333–337.
- Jensen, M. K., Andersen, A. T., Sorensen, T. I., Becker, U., Thorsen, T., and Gronbaek, M. (2002). Alcoholic beverage preference and risk of becoming a heavy drinker. *Epidemiology* *13*, 127–132.
- Johnson, B. A., Cloninger, C. R., Roache, J. D., Bordnick, P. S., and Ruiz, P. (2000). Age of onset as a discriminator between alcoholic subtypes in a treatment-seeking outpatient population. *Am. J. Addict.* *9*, 17–27.
- Johnson, B. A., Koob, G. F., Schuckit, M. A., Mason, B. J., and Ait-Daoud, N. (2006). Understanding and treating alcohol dependence. *Alcohol Clin. Exp. Res.* *30*, 567–584.
- Kerr, W. C., Fillmore, K. M., and Marvy, P. (2000). Beverage-specific alcohol consumption and cirrhosis mortality in a group of English-speaking beer-drinking countries. *Addiction* *95*, 339–346.
- Kiefer, F., Andersohn, F., Jahn, H., Wolf, K., Raedler, T. J., and Wiedemann, K. (2002). Involvement of plasma atrial natriuretic peptide in protracted alcohol withdrawal. *Acta Psychiatr. Scand.* *105*, 65–70.
- Kiefer, F., Jimenez-Arriero, M. A., Klein, O., Diehl, A., and Rubio, G. (2008). Cloninger's typology and treatment outcome in

- alcohol-dependent subjects during pharmacotherapy with naltrexone. *Addict. Biol.* 13, 124–129.
- Klatsky, A. L., Friedman, G. D., Armstrong, M. A., and Kipp, H. (2003). Wine, liquor, beer, and mortality. *Am. J. Epidemiol.* 158, 585–595.
- Kripalani, S., Yao, X., and Haynes, R. B. (2007). Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch. Intern. Med.* 167, 540–550.
- Lachenmeier, D. W., Haupt, S., and Schulz, K. (2008). Defining maximum levels of higher alcohols in alcoholic beverages and surrogate alcohol products. *Regul. Toxicol. Pharmacol.* 50, 313–321.
- McLellan, A. T., Lewis, D. C., O'Brien, C. P., and Kleber, H. D. (2000). Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* 284, 1689–1695.
- Moak, D. H., Anton, R. F., and Latham, P. K. (1998). Further validation of the Obsessive-Compulsive Drinking Scale (OCDS). Relationship to alcoholism severity. *Am. J. Addict.* 7, 14–23.
- Morris, P. L., Hopwood, M., Whelan, G., Gardiner, J., and Drummond, E. (2001). Naltrexone for alcohol dependence: a randomized controlled trial. *Addiction* 96, 1565–1573.
- Naimi, T. S., Brewer, R. D., Miller, J. W., Okoro, C., and Mehrotra, C. (2007). What do binge drinkers drink? Implications for alcohol control policy. *Am. J. Prev. Med.* 33, 188–193.
- Norström, T. (1998). Effects on criminal violence of different beverage types and private and public drinking. *Addiction* 93, 689–699.
- Raistrick, D., Dunbar, G., and Davidson, R. (1983). Development of a questionnaire to measure alcohol dependence. *Br. J. Addict.* 78, 89–95.
- Rimm, E. B., and Stampfer, M. J. (2002). Wine, beer, and spirits: are they really horses of a different color? *Circulation* 105, 2806–2807.
- Saffroy, R., Benyamina, A., Pham, P., Marill, C., Karila, L., Reffas, M., et al. (2008). Protective effect against alcohol dependence of the thermolabile variant of MTHFR. *Drug Alcohol Depend.* 96, 30–36.
- Sakuta, H., Suzuki, T., Ito, T., and Yasuda, H. (2007). Beer ethanol consumption and plasma homocysteine among patients with type 2 diabetes. *Diabetes Res. Clin. Pract.* 78, 202–207.
- Schlienger, J. L. (2003). Homocysteine and alcohol consumption. An ambiguous relationship and a new paradox. *Presse Med.* 32, 262–267.
- Sinha, R., and O'Malley, S. S. (1999). Craving for alcohol: findings from the clinic and the laboratory. *Alcohol Alcohol.* 34, 223–230.
- Strandberg, T. E., Strandberg, A. Y., Salomaa, V. V., Pitkala, K., Tilvis, R. S., and Miettinen, T. A. (2007). Alcoholic beverage preference, 29-year mortality, and quality of life in men in old age. *J. Gerontol. A. Biol. Sci. Med. Sci.* 62, 213–218.
- Swift, R., and Pettinati, H. M. (2005). Choosing pharmacotherapies for the COMBINE Study—process and procedures: an investigational approach to combination pharmacotherapy for the treatment of alcohol dependence. *J. Stud. Alcohol.* 140, 141–147.
- Volcik, K. A., Ballantyne, C. M., Fuchs, F. D., Sharrett, A. R., and Boerwinkle, E. (2008). Relationship of alcohol consumption and type of alcoholic beverage consumed with plasma lipid levels: differences between Whites and African Americans of the ARIC study. *Ann. Epidemiol.* 18, 101–107.
- Volpicelli, J. R. (2001). Alcohol abuse and alcoholism: an overview. *J. Clin. Psychiatry* 62, S4–10.
- Watt, K., Purdie, D. M., Roche, A. M., and McClure, R. J. (2004). Risk of injury from acute alcohol consumption and the influence of confounders. *Addiction* 99, 1262–1273.
- Weiss, R. D., and Kueppenbender, K. D. (2006). Combining psychosocial treatment with pharmacotherapy for alcohol dependence. *J. Clin. Psychopharmacol.* 26, S37–42.
- Wilhelm, J., Frieling, H., Hillemecher, T., Degner, D., Kornhuber, J., and Bleich, S. (2008). Hippocampal volume loss in patients with alcoholism is influenced by the consumed type of alcoholic beverage. *Alcohol Alcohol.* 43, 296–299.
- World Health Organization (WHO) (1992). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization.
- World Health Organization (WHO) (2006). *Regional Office for the Eastern Mediterranean. Public Health Problems of Alcohol Consumption in the Region*. Geneva: World Health Organization.
- Yoon, G., Kim, S. W., Thuras, P., Grant, J. E., and Westermeyer, J. (2006). Alcohol craving in outpatients with alcohol dependence: rate and clinical correlates. *J. Stud. Alcohol.* 67, 770–777.