

## ORIGINAL ARTICLE

### Prognostic Factors During Outpatient Treatment for Alcohol Dependence: Cohort Study with 6 months of Treatment Follow-up

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**Abstract — Aims:** To identify prognostic factors to outpatient alcohol treatment on admission as well as during the treatment period. **Methods:** A cohort study of  $n=209$  alcoholic patients (DSM-IV) during 6 months of outpatient treatment. Eight medical doctors from two hospitals were involved. Co-responsible participation in treatment was a necessary condition. At admission, we documented socio demographic factors, use of other drugs and severity of alcohol consumption. During the 6 months, we observed medication for prevention of alcohol relapse [disulfiram (DIS), acamprosate], number of sessions with the doctor, number of phases of the consultation and medication for depression. Primary outcome variables were time to first heavy relapse and abstinence of heavy alcohol consumption. These were measured with Timeline Followback. Five or more alcohol units of 10 g in one relapse day were considered heavy relapse. **Results:** The patients were 84% males, with 41 years median age; the median alcohol consumption was 192 g per day with a median duration of 13 years of heavy consumption. The median education was 6 years with 61% of the patients from lower socio-economic levels. The Kaplan–Meier heavy relapse rate at 6 months was 23%. On admission to treatment, female gender, lower socio-economic levels, cocaine use, >20 years of consumption, gamma glutamyl transferase values above normal and five or more alcohol-related problems on the Alcohol-Related Problem Questionnaire predicted worse outcomes. Having a full-time job and shorter abstinence time before treatment (until 7 days) predicted better outcomes. During the 6 months, we found that DIS for <120 days was a prognostic factor of worse outcomes. DIS for at least 120 days, >50% of adherence to consultations and more than two phases on each consultation predicted better outcomes. The combined sensitivity and specificity for DIS for at least 120 days, >50% of adherence to consultations and more than two phases on consultation regarding abstinence from heavy relapse were respectively 100 and 71%. **Conclusions:** During 6 months of outpatient treatment, longer adherence to DIS and consultations as well as more phases in a consultation involving necessarily a co-responsible predict a good outcome independently of the patient features at admission.

## INTRODUCTION

The World Health Organization ranked alcohol as the third most important risk factor for the increase in the number of disability-adjusted life years in Portugal, as well as in Europe, preceded by tobacco smoking (second risk factor) and hypertension (first risk factor) (WHO, 2005).

Portugal is a country with a traditional culture of wine production and consumption.

Nearly, 7% of the population aged 15 years or more is alcohol dependent (Gameiro, 1998; Mello *et al.*, 2001; Direcção Geral de Saúde, 2004). The mean alcohol consumption of male drinkers in the general population is 47.3 g per day and 17.1 g for female drinkers (Marques-Vidal and Dias, 2005), alcohol dependence in Portugal being more prevalent in males than in females (ratio 8 to 1: Gameiro, 1998).

About 6 of 10 patients with alcohol dependence will relapse in the 6 months following detoxification, as estimated by the median of 61% relapse rate obtained in several studies (Elis and McClure, 1992; Barrias *et al.*, 1997; Besson *et al.*, 1998; Chick *et al.*, 2000; Curran *et al.*, 2000; Rubio *et al.*, 2001; Neto *et al.*, 2007; Nielsen *et al.*, 2007; Terra *et al.*, 2008). This high rate of relapse in a relatively short period is a reason for searching for the factors that better predict treatment outcomes.

Several treatment baseline factors were studied suggesting that professional and marital stability are associated with good prognosis (Waisberg, 1990; Glenn and Parsons, 1991; McKay and Weiss, 2001; Walton *et al.*, 2003; Bottlender and Soyka, 2005a; Moos and Moos, 2006; Walter *et al.*, 2006; Terra *et al.*, 2008). Besides this, low education level and

lower socio-economic level suggest worse prognosis (McKay and Weiss, 2001; Moos and Moos, 2006; Ilgen *et al.*, 2007). More age at treatment admission is generally a good prognostic factor (McKay and Weiss, 2001; Gordon *et al.*, 2006; Moos and Moos, 2006; Chong and Lopez, 2008). The results for gender are contradictory revealing female gender associated with good prognostics (Rounsaville *et al.*, 1987; McKay and Weiss, 2001; Gordon *et al.*, 2006; Moos and Moos, 2006) as well as bad prognostics (Ellis and McClure, 1992; Bottlender and Soyka, 2005b).

According to Staines *et al.* (2003), >60% of alcohol-dependent patients use other drugs such as cocaine, heroin and cannabis. The literature suggests contradictory results such as drug use at treatment baseline associated with worse treatment outcomes (Rounsaville *et al.*, 1987) or drug use associated with better outcomes (Chong and Lopez, 2008).

In respect of alcohol severity at treatment baseline, several authors suggest that worse severity is associated with worse prognostics (McLellan *et al.*, 1994; McKay and Weiss, 2001; Staines *et al.*, 2003; Bottlender and Soyka, 2005a; Moos and Moos, 2006; Ilgen *et al.*, 2007), but it was mentioned as well that severity could be a prognostic factor of good outcomes, certainly for motivational reasons (Waisberg, 1990; McKay and Weiss, 2001; Staines *et al.*, 2003).

During the treatment period, the efficacy of pharmacological drugs for relapse prevention such as disulfiram (DIS), acamprosate (ACA) and naltrexone is well documented (Chick *et al.*, 1992; Barrias *et al.*, 1997; Besson *et al.*, 1998; Tempesta *et al.*, 2000; Streeton and Whelan, 2001; Guardia *et al.*, 2002; Niederhofer and Staffen, 2003; Kiritzé-Topor

*et al.*, 2004; Mann *et al.*, 2004; Kiefer *et al.*, 2005; Verheul *et al.*, 2005; Feeney *et al.*, 2006; Laaksonen *et al.*, 2007; Neto *et al.*, 2007). Treatment adherence is important (McKay and Weiss, 2001; Kiritzé-Topor *et al.*, 2004) including the adherence to medical consultations during treatment (McCrary and Epstein, 2004; Mann *et al.*, 2005; Terra *et al.*, 2008). Also, the style of the consultation matters: involving the patient co-responsible in the consultation at a number of separate points (Neto *et al.*, 2008).

Alcoholic anonymous (AA) participation predicted good outcomes in studies (Ellis and McClure, 1992; McKay and Weiss, 2001; Room *et al.*, 2005; Ilgen *et al.*, 2007; Terra *et al.*, 2008).

Depression was as a bad prognostic factor in some studies (Glenn and Parsons, 1991; Ellis and McClure, 1992; Greenfield *et al.*, 1998; Curran *et al.*, 2000; Staines *et al.*, 2003; Bottlender and Soyka, 2005a,b). But in other studies, depression at baseline also proved to be associated with favourable outcomes (Terra *et al.*, 2008).

With this background, we set as the general study objective the role of each of the aforementioned factors in the prognosis of outpatient treatment in a sample of alcoholic patients treated in the public sector in Lisbon, Portugal.

## METHODS

### *Design*

The study was conducted in an observational clinical cohort of alcohol-dependent patients followed during 6 months of outpatient treatment (follow-up period). The sample comprised 209 patients selected according to Diagnostic and Statistical Manual of Mental Disorders DSM-IV (APA, 1994; APA, 2002) in two hospital centers: *Unidade de Alcoologia de Lisboa* ( $n = 194$ ) and *Hospital Nossa Senhora do Rosário* ( $n = 15$ ), being the data collection authorized by institution ethical approval (Neto *et al.*, 2008).

The responsibility for a patient's treatment was taken by one of eight medical doctors, of whom six were male, and whose professional experience was between 14 and 31 years (average experience of 24 years). The tradition in these hospitals is that medical doctors see the patient from the outset and offer regular medical consultations to prevent relapse, sometimes also involving a psychologist or a social worker.

A necessary condition for entry to this study was the availability of a co-responsible person (usually a family member) to provide information to the researchers and assist with the maintenance of abstinence.

The patients were sequentially and randomly assigned to either 'sequential combined treatment' or 'treatment as usual'. The sequential combined treatment uses up to four phases in one of the consultations: the first phase with the patient and the co-responsible, the second with the patient alone, the third phase with the co-responsible alone and the fourth phase with the patient and the co-responsible again. Treatment as usual uses up to two phases in one consultation: the first phase with the patient alone and sometimes a second phase with patient and the co-responsible. The effectiveness of the sequential combined treatment in comparison with the usual treatment was shown previously by Neto *et al.* (2008). With the three or four phases, the length of the consultations was no >30 min. Each patient was invited to make seven clinic visits during the six treatment months.

### *Patient selection*

The co-responsible persons were husband/wife in 61% of cases; the others were close friends, colleagues, social workers or justice officers. All patients and their co-responsible signed an informed consent to participate in the study. The co-responsible assumed the role of key informant as well as collaborator in the treatment. When requested by the doctor and accepted by the patient, the co-responsible had the responsibility of observing the ingestion of DIS by the patients.

The patients included had to be abstinent for at least 24 h without signs of withdrawal syndrome. Patients were excluded from the study if they had severe psychiatric or physical co-morbidity, active co-morbidity associated with substances other than tobacco, previous allergic reactions to DIS and de-compensated hepatic disease, or were illiterate.

### *Prognostic factors at baseline*

At admission to treatment, we recorded the basic demographics, including socio-economic level (Graffard, 1956), status of co-responsible, stable sexual and emotional relationship, family and social situation; past use of illicit drugs, benzodiazepines and past or actual tobacco smoking.

To measure severity of alcohol consumption, we recorded years of heavy consumption—defined as 50 g per day or more—alcohol quantity in grams per typical day, abstinence days previous to admission, favorite drink (fortified beverages and liquors, wine and beer), pattern of consumption (daily versus weekend or episodic), morning drinking, presence of previous treatments for alcohol dependence, maximum previous abstinence duration.

With respect to severity of alcoholism, we also measured concentrations of serum gamma glutamyl transferase (GGT), alanine amino transferase (ALT), aspartate amino transferase (AST) and mean red cell volume (MCV), higher values on these blood measures representing higher severity (Deguti and Gonçalves, 2000). The values were normalized by the ratio between the value and the laboratory cut-off, so that relevant increased clinical values were represented by values greater than 1.

The Alcohol-Related Problems Questionnaire (ARPQ) was applied to the measurement of eleven binary variables on admission to treatment as well as the sum score of all problems (Patience *et al.*, 1997).

The seven diagnostic criteria for alcohol dependence (DSM-IV) measured on admission to treatment were also considered binary variables for prognostic factor analysis as well as the sum between 3 and 7 scores, 3 being the minimum number of criteria observed for a person to be assumed as dependent (APA, 1994, 2002).

### *Prognostic factors measured during treatment*

During the 6-month treatment period, prescription of DIS and ACA and their days of intake were documented. The daily dose of DIS was 125/250 mg and ACA 1332/1998 mg. Doctors choosing between DIS and ACA did not follow any patient severity criteria.

The adherence to consultations was measured. Phases of consultation (1–4) were measured as an average within patient, computed as the sum of the phases in all consultations divided by the number of consultations made by the patient.

Other factors measured during the treatment period were AA participation (at least one session) and the prescription of antidepressants as well as their days of intake. The antidepressants prescribed were sertraline, venlafaxine and mirtazapine.

#### Outcome variables

- (a) Time to heavy relapse was defined as the number of days from treatment start until the first consumption of five or more standard drinks in one occasion (Greenfield *et al.*, 1998; Rubio *et al.*, 2001; Guardia *et al.*, 2002; Johnson *et al.*, 2003; De Sousa and De Sousa, 2004, 2005; Kiefer *et al.*, 2005; Laaksonen *et al.*, 2007). A standard drink was that containing 10 g of alcohol, which in Portugal is a glass of beer, a glass of wine or a measure of distilled alcohol beverage (Babor *et al.*, 2001). Lost to follow-up was analyzed as censored time.
- (b) Absence of heavy relapse during the 6 months was defined as 'yes/no'; for lost-to-follow-up cases, the worst-case scenario was used (Barrias *et al.*, 1997; Besson *et al.*, 1998; De Sousa and De Sousa, 2004; Bottlender and Soyka, 2005a).
- (c) Abstinence from all alcohol consumption during the 6 months was defined as yes/no; for lost-to-follow-up cases, the worst-case scenario was used (Barrias *et al.*, 1997; Besson *et al.*, 1998; Mann *et al.*, 2004; Bottlender and Soyka, 2005a,b; Verheul *et al.*, 2005; Feeney *et al.*, 2006; Walter *et al.*, 2006).
- (d) Cumulative abstinence duration (CAD) was the sum of all abstinent days during the 6 months (Barrias *et al.*, 1997; Besson *et al.*, 1998; Feeney *et al.*, 2006; Laaksonen *et al.*, 2007); for statistical analysis dichotomized in two categories: equal/above or below the sample observed mean of 131 days CAD.
- (e) Longest relapse duration (days) was dichotomized in the categories longest relapse above 1 day versus 0 or 1 day longest relapse.
- (f) Having accumulated at least one problem in ARPQ during the treatment period was documented at month 6 as a binary outcome variable (Kiritzé-Topor *et al.*, 2004).

All the outcome variables representing alcohol consumption and relapse were recorded in a self-reported Timeline Followback (TLFB) (Sobell and Sobell, 1992), one of the more accurate methods for estimation of alcohol consumption (Del Boca and Darkes, 2003). Two research assistants blind to the treatment method applied the TLFB using telephone interviews to patients and their co-responsibles at 15-day intervals. For cases where patients and co-responsibles differed, interviewers assumed the most pessimistic version and a final validation made by researchers, through comparisons between TLFB and the clinical process of the patient, assuming again the most pessimistic version.

#### Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS V18). The significance level was assumed at 5% in bilateral hypothesis tests and 95% confidence intervals (CIs) were also used.

Area under the ROC curve (receiver operating characteristic) was computed to analyze the relationship between numerical prognostic factors and binary outcomes (Hosmer and Lemeshow, 1998).

Kaplan–Meier survival analysis was used to analyze the relationship between prognostic factors and time to first heavy relapse (Pocock, 1983).

Multiple Cox regression was used to compute the adjusted hazard ratios (HRs) between each simultaneous prognostic factors and time to first heavy relapse (Kleinbaum and Klein, 2005; Rothman *et al.*, 2008).

Multiple logistic regression was used to compute adjusted odds ratios (OR) between each simultaneous prognostic factors and a binary outcome (Hosmer and Lemeshow, 1998; Rothman *et al.*, 2008).

From all independent prognostic factors considered, we selected a restricted set for multivariable analysis. These variables were selected according to the following criteria:  $P < 0.10$  in bivariable analysis for at least one outcome variable and non-evidence of co-linearity. Backward selection controlled by researcher in each step was used to optimize the regression modelling.

Sensitivity and specificity analysis was done between several prognostic factors and the mentioned binary outcomes.

## RESULTS

#### Patients' characteristics at baseline

In the sample of 209 was 84% male, of median age 41 (min–max: 21–62), median education 6 years (min–max: 2–17), with 61% in the lowest socio-economic levels (Graffard's IV and V).

The median alcohol consumption in a typical day was 192 g (min–max: 35–1080), with a 13 year median duration of heavy alcohol consumption (min–max: 1–39). About 15, 11, 11 and 10% of the patients reported past use, respectively, of cannabis, benzodiazepines, heroin and cocaine; 69% of the patients were current smokers or ex-smokers; 51% of the patients had previous treatments for alcohol dependence and 18% had had previous inpatient treatment.

About 54, 38, 41 and 30% of the patients had increased values for GGT, AST, ALT and MCV.

The median number of problems from ARPQ was 5 (min–max: 0–11); the median number of criteria for alcohol dependence from DSM-IV was 7 (min–max: 3–7).

#### Possible prognostic factors arising during treatment

About 82% of patients had DIS prescribed [median intake 179 days (min–max: 7–180); 72% had taken it for 120 days or more]. Only 14% of patients had ACA prescribed: 28% took it during 120 days or more with a median intake of 90 days (min–max: 20–180). About 10% of the patients had prescriptions for DIS and ACA simultaneously; 87% of patients had prescription for at least one of these two medications.

The median number of visits made by the patient was 4 (min–max: 1–7). The median number of consultation phases within visits was 1.8 (min–max: 1–4); 40% had 2.5 phases or more at visits. AA was attended (at least one meeting) by 18%.



About 33% of the patients had anti-depressants prescribed [median intake of 180 days (min–max: 15–180)].

### Prognostic factors analysis

The Kaplan–Meier heavy relapse rate was 23% CI (95%) = (16–29%); relapse rate for any alcohol quantity was 54% CI (95%) = (47–60%). The mean of the CAD was 131 days CI (95%) = (122–140).

Table 1, bivariable analysis, shows only the independent variables included in multivariable analysis that achieved statistical significance or at least reached  $P < 0.10$  after multivariable optimization. The final results of the multivariable analysis after statistical optimization, as well as adjusted effect measures are shown in Table 2 and show that on admission to treatment female gender predicted worse outcomes; lower socio-economic status predicted worse outcomes; a full-time job predicted better outcomes, past use of cocaine predicted worse outcomes; >20 years of excessive alcohol consumption predicted worse outcomes; patients with a shorter period of abstinence before treatment, say up to 7 days, were likely to have better outcomes; a greater severity of dependence as indicated by morning or before lunch consumption predicted better outcomes; liver severity indicated by GGT predicted worse outcomes; patients with five or more alcohol-related problems on ARPQ at admission showed worse outcomes.

Multiple regression techniques showed that taking DIS for 120 days at least predicted better outcomes; taking DIS for less than 120 days predicted worse outcomes regarding all the six outcome variables; ACA prescription predicted worse outcomes; attending four or more visits predicted better outcomes; having a mean of 2.5 or more phases in a consultation predicted better outcomes.

The most important predictors from the treatment itself of favourable outcomes were the number of days of taking DIS, adherence to consultations and phases of each consultation. Regarding heavy relapse, we found areas under ROC curve of 0.93 ( $P < 0.001$ ), 0.82 ( $P < 0.001$ ) and 0.68 ( $P < 0.001$ ), respectively for days DIS taken for patients with a DIS prescription, number of consultations made and average of consultation phases. Considering a cut-off of 120 days of taking DIS, we found that 120 or more days of DIS had a sensitivity and a specificity of 97 and 68%, respectively, for avoiding heavy relapse in patients with a DIS prescription. Attending >50% of the seven consultations offered (i.e. four or more consultations) had a sensitivity and a specificity, respectively, of 92 and 63% for avoiding heavy relapse. At least a 2.5 average consultation phases allows a sensitivity and a specificity of 56 and 77%, respectively for avoiding heavy relapse.

A patient with a DIS prescription who took DIS for at least 120 days and attended >50% of the total consultations (four consultations), the sensitivity and the specificity for abstinence of heavy drinking are 100 and 61%, respectively ( $n = 121$  analyzed patients that made DIS  $\geq 120$  and consultations  $\geq 4$  versus DIS  $< 120$  and consultations  $< 4$  simultaneously). If we add at least 2.5 phases of consultation to this analysis ( $n = 77$  patients that made DIS  $\geq 120$  and consultations  $\geq 4$  and phases  $\geq 2.5$  versus DIS  $< 120$  and consultations  $< 4$  and phases  $< 2.5$  simultaneously), we get the same sensitivity of 100% and improve the specificity to 71%.

### Other association results found

Women in comparison with men had more antidepressant prescriptions (58 versus 28%;  $P = 0.001$ ) and a higher rate of antidepressant use (i.e. for 120 days or more) (30 versus 15%;  $P < 0.01$ ). For patients with alcohol consumption for 20 years, the number of years of heavy consumption was positively correlated with CAD (Spearman's  $R_s = 0.30$ ;  $P < 0.01$ ), as well as negatively correlated with the maximum days of relapse (Spearman's  $R_s = -0.19$ ;  $P < 0.05$ ). Patients with raised GGT levels had a more prominent pattern of daily consumption in comparison with patients with normal GGT (96 versus 89%;  $P < 0.05$ ), and patients who drank in the morning and before lunch had higher GGT (median of 1.3 versus 0.89;  $P < 0.05$ ) levels. Patients with raised GGT levels were more likely to report all the seven alcohol dependence criteria from DSM-IV (61 versus 44%;  $P < 0.05$ ).

For patients with a DIS prescription, the number of days of DIS intake was positively correlated with the number of visits made by the patient (Spearman's  $R_s = 0.47$ ;  $P < 0.01$ ). Patients who had DIS or ACA prescription had at baseline a higher alcohol median quantity on a typical day (192 versus 155 g;  $P < 0.05$ ).

## DISCUSSION

This research identifies prognostic factors in a short-period follow-up; this is in line with others who advocate the importance of short-term prognosis (Glenn and Parsons, 1991; McKay and Weiss, 2001; Room *et al.*, 2005).

In this study, relapse to heavy drinking (Kaplan–Meier cumulative incidence) showed a very favourable rate of 23% at 6 months. Even according to the worst-case scenario, the rate of relapse to any alcohol was 54%, but this is lower than the 61% median relapse rate reported in several studies of alcohol treatment (Ellis and McClure, 1992; Barrias *et al.*, 1997; Besson *et al.*, 1998; Chick *et al.*, 2000; Curran *et al.*, 2000; Rubio *et al.*, 2001; Neto *et al.*, 2007; Nielsen *et al.*, 2007; Terra *et al.*, 2008). Two possible explanations are the relatively good social support of our patients (70% had a stable relationship and 92% were not living alone) and the power of the treatments employed.

That the female gender was associated with worse prognosis in this study is consistent with many other studies (Ellis and McClure, 1992; Walton *et al.*, 2003; Bottlender and Soyka, 2005a,b; Neto *et al.*, 2007). Some authors attribute this to higher prevalence of comorbid depression and anxiety (Rounsaville *et al.*, 1987; Waisberg, 1990; Ellis and McClure, 1992; Callaghan and Cunningham, 2002; Kusner *et al.*, 2005) in females. We found that women compared with men had a higher rate of prescription and days of antidepressants taken, and a (non-significant) higher rate of depression attributed to alcohol in the ARPQ. However, when we introduced into a multiple regression model the variable 'days of antidepressant intake', female gender was still associated with a worse prognosis. This result suggests for this study population that being women could be a factor of poor prognosis independent of depression, at least in Portugal.

Lower socio-economic levels and more precarious professional situation emerged as poor prognostic factors (c.f. Waisberg, 1990; Ellis and McClure, 1992; McKay and

Table 1. Bivariable analysis of the prognostic factors included in multivariable analysis—6-month follow-up (maximum  $n = 209$ )

Prognostic factor ( $n =$ )	Variable categories (.)	Kaplan–Meier cumulative survival rate ( $n = 209$ )	Abstinence rate of heavy drink ( $n = 209$ )	Abstinence rate of any alcohol consumption ( $n = 209$ )	Rate of cumulative abstinence duration above the mean of 131 days ( $n = 209$ )	Rate of longest duration of relapse above 1 day ( $n = 156$ )	Rate of having at least one problem in ARPQ at 6 months ( $n = 192$ )
Sex ( $n = 209$ )	Male (176)	78.1%	55.7%	48.9%	67.0%	24.1%	40.4%
	Female(33)	72.2%	36.4%*	33.3%	51.5%++	36.8%	58.1%++
Graffard's socio-economic level ( $n = 209$ )	Upper and middle level I, II, III (81)	77.4%	61.7%	53.1%	72.8%	21.5%	33.8%
	Lower level IV, V (128)	77.3%	46.9%*	42.2%	59.4%*	28.6%	49.2%*
Professional situation ( $n = 209$ )	Without full-time job (109)	74.7%	45.0%	41.3%	60.6%	29.3%	50.5%
	With full-time job (100)	79.6%	61.0%*	52.0%	69.0%	22.2%	35.2%*
Past use of cocaine ( $n = 209$ )	Without use (188)	77.9%	55.3%	50.0%	67.0%	26.0%	40.9%
	With use (21)	70.5%	28.6%*	14.3%**	42.9%*	20.0%	61.9%++
Years of heavy alcohol consumption ( $n = 209$ )	≤10 years (95)	76.6%	46.3%	40.0%	56.8%	26.6%	47.7%
	11–20 years (83)	77.8%	65.1%	60.2%	79.5%	19.7%	32.1%
	>20 years (31)	79.3%	38.7%*	29.0%**	48.4%***	42.9%++	60.7%*
Abstinence days before treatment ( $n = 209$ )	>7 days (137)	72.9%	46.7%	42.3%	61.3%	26.3%	48.8%
	1–7 days (72)	85.1%	63.9%*	54.2%	70.8%	24.6%	33.3%*
Morning or before lunch drinking ( $n = 209$ )	Does not drink (53)	84.0%	47.2%	35.8%	60.4%	23.5%	46.9%
	Drinks (156)	75.3%	54.5%	50.0%++	66.0%	26.2%	42.0%
GGT ( $n = 193$ )	Normal (≤1) (88)	81.8%	52.3%	47.7%	63.6%	27.5%	42.0%
	Increased (>1) (105)	72.9%++	57.1%	49.5%	70.5%	24.4%	39.2%
ARPQ sum (0–11) ( $n = 192$ )	Lower than five problems (70)	88.3%	68.6%	62.9%	82.9%	10.7%	28.6%
	Five or more problems (122)	74.5%*	45.9%**	38.5%***	54.9%***	30.2%**	51.6%***
Days of DIS intake ( $n = 186$ )	0 days (38)	87.9%	44.7%	44.7%	55.3%	17.4%	57.9%
	<120 days (42)	45.7%	7.1%	7.1%	21.4%	60.9%	83.8%
	≥120 days (106)	87.6%***	83.0%***	71.7%***	97.2%***	17.6%***	11.5%***
The presence of ACA prescription ( $n = 209$ )	Not done ACA (179)	80.4%	52.5%	46.9%	63.7%	21.7%	44.2%
	Did ACA (30)	61.2%*	53.3%	43.3%	70.0%	44.4%*	37.9%
Adherence to doctors consultations (1–7) ( $n = 209$ )	1–3 (71)	67.4%	12.7%	12.7%	16.9%	42.9%	86.4%
	4–7 (138)	81.5%***	73.2%***	63.8%***	89.1%***	21.9%*	20.6%***
Average of consultation phases (1–4) ( $n = 209$ )	<2.5 Phases(125)	68.3%	39.2%	35.2%	54.4%	38.4%	54.4%
	≥2.5 Phases (84)	89.3%***	72.6%***	63.1%***	79.8%***	10.0%***	26.9%***
			ROC = 0.68***	ROC = 0.65***	ROC = 0.64***	ROC = 0.69***	ROC = 0.66***

\* $P < 0.05$  on Log-rank test for survival curves comparison or chi-square/Fisher exact test for group comparison or test of area under the ROC = 0.50.

\*\* $P < 0.01$ .

\*\*\* $P < 0.001$ .

++ $P < 0.10$ , (.), maximum number of cases within a category of a prognostic factor; ROC, area under the ROC curve (always area >0.50 according to code 1 or 0 of the binary outcome); %, outcome rate within comparative group, (s), ROC curve computed for the subsample with days of medication took >0.

Table 2. Prognostic factor results from multivariable regression analysis (Cox and Logistic) at a 6-month follow-up

Prognostic factor	Variable categories	Time to heavy relapse (five or more drinks in a day) ( <i>n</i> = 176) HR	Abstinence of heavy drink (days with less than five alcohol units) ( <i>n</i> = 186) OR	Abstinence from any alcohol consumption ( <i>n</i> = 186) OR	Cumulative abstinence duration above the mean of 131 days ( <i>n</i> = 171) OR	Duration of longest relapse above 1 day ( <i>n</i> = 135) OR	Having at least one problem in ARPQ at 6 months ( <i>n</i> = 171) OR
Sex	Male REF	—	—	—	—	1	—
	Female	—	—	—	—	4.551*	—
Graffard's socio-economic level	Upper and middle level (I, II, III) REF	—	1	1	1	—	—
	Lower level (IV, V)	—	0.324*	0.414*	0.054**	—	—
Professional situation	Without full-time job REF	—	—	—	—	—	1
	With full-time job	—	—	—	—	—	0.368*
Past use of cocaine	Without use REF	—	1	1	1	—	—
	With use	—	0.110**	0.051***	0.112++	—	—
Years of heavy alcohol consumption	≤10 years REF	—	—	1	1	1	1
	11–20 years	—	—	1.288	2.880	1.544	1.243
	>20 years	—	—	0.199*	0.051*	8.360**	7.319**
Abstinence days prior to treatment	>7 days REF	1	1	—	—	—	—
	1–7 days	0.387*	2.662++	—	—	—	—
Morning or before lunch drinking	Does not drink REF	—	—	1	—	—	—
	Drinks	—	—	3.012*	—	—	—
GGT	Normal (≤1) REF	1	—	—	—	—	—
	Increased (>1)	2.295*	—	—	—	—	—
ARPQ sum (0–11)	Lower than five problems REF	—	—	—	1	1	—
	Five or more problems	—	—	—	0.036**	2.577++	—
Days of DIS intake	0 days REF	1	1	1	1	1	1
	<120 days	12.613***	0.062***	0.050***	0.084*	15.600**	5.246*
	≥120 days	2.893	1.793	0.820	18.877**	3.133	0.163***
Presence of ACA prescription	Not done ACA REF	1	—	—	—	1	—
	Did ACA	2.806*	—	—	—	2.742++	—
Adherence to doctors consultations (1–7)	1–3 REF	—	1	1	1	—	1
	4–7	—	9.097***	5.556***	177.5***	—	0.074***
Average of consultation phases (1–4)	<2,5 Phases REF	1	1	1	—	1	—
	≥2,5 Phases	0.268**	2.800*	3.242*	—	0.207**	—
Model <i>P</i> value	—	<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> <0.001
Hosmer–Lemeshow <i>P</i> -value	—	—	<i>P</i> =0.77	<i>P</i> =0.52	<i>P</i> =0.71	<i>P</i> =0.50	<i>P</i> =0.11
Model area under ROC curve and <i>P</i> -value	—	—	90%, <i>P</i> <0.001	88%, <i>P</i> <0.001	98%, <i>P</i> <0.001	82%, <i>P</i> <0.001	91%, <i>P</i> <0.001

HR, hazard ratio adjusted for co-variables by multiple Cox regression; OR, odds ratio adjusted for co-variables by multiple logistic regression; REF, reference category for comparison.

\**P*<0.05 Wald test.

\*\**P*<0.01 Wald test.

\*\*\**P*<0.001 Wald test.

++*P*<0.10 Wald test.

Weiss, 2001; Walton *et al.*, 2003; Bottlender and Soyka, 2005a,b; Moos and Moos, 2006; Ilgen *et al.*, 2007).

Previous cocaine predicted worse prognosis (c.f. Rounsaville *et al.*, 1987; Callaghan and Cunningham, 2002).

Considering severity of alcohol consumption, it was found that heavy consumption over 20 years, having a raised serum GGT level and having at least 5 of the 11 problems of ARPQ predicted poor outcomes, use for >20 years being the most important prognostic factor in number of statistically significant results, namely in four of the six outcome variables. A more severe history of alcohol consumption associated with a worse prognosis is expected from previous studies (Rounsaville *et al.*, 1987; McLellan *et al.*, 1994; McKay and Weiss, 2001; Staines *et al.*, 2003; Bottlender and Soyka, 2005a; Moos and Moos, 2006; Ilgen *et al.*, 2007). An important aspect of the duration of alcohol consumption in this study is that prognosis improves with duration of use up to 20 years, after which this trend is reversed. It was found with statistical significance for patients with alcohol consumption for up to 20 years that the number of years of consumption was positively correlated with CAD as well as negatively correlated with the maximum duration of relapses. This suggests that as duration of alcohol consumption increases until a certain cut-off, say 20 years, it also increases the likelihood of better prognosis naturally associated with an increased age of the patients.

Raised serum GGT level at baseline was important, particularly as a predictor of time to the first heavy relapse. Higher GGT level was associated with a pattern of daily consumption, as well as drinking in the morning, which in turn are two important indicators of the severity of consumption (Stockwell *et al.*, 1983; Ellis and McClure, 1992; Babor *et al.*, 2001; Ilgen *et al.*, 2007). Also, GGT level was associated with meeting the seven DSM-IV criteria for diagnosis of alcoholism, another possible indicator of severity (Schuckit *et al.*, 1997). Thus, it appears that GGT level is an important prognostic factor reflecting severity and should be taken into account in alcohol studies.

Less expected was the fact that patients with morning or before-lunch alcohol consumption had better prognosis, since drinking in the morning or before lunch is an indicator of severity of consumption (Stockwell *et al.*, 1983; Babor *et al.*, 2001). One possible explanation for this is that patients with more severity in some indicators may also have greater motivation to recover from their alcohol problems and consequently adhere better to treatment. In this sense, some authors suggest that higher levels of severity of patients at admission to treatment can be associated with better prognosis after treatment (Waisberg, 1990; McKay and Weiss, 2001).

An important result was that patients who entered treatment with a shorter period of abstinence, say up to a week, had a better prognosis than patients with more abstinent days before treatment. Motivation of patients to initiate a formal and longer treatment may be highest during or soon after detoxification. Chick *et al.* (2000) offered as one explanation for the ineffectiveness of drug treatment in their study the fact that there had been a long time, even several weeks, between detoxification and the start of drug treatment for many patients.

The advantage of taking DIS for at least 120 days is consistent with other reports of supervised DIS (Chick *et al.*, 1992; Mello *et al.*, 2001; Niederhofer and Staffen, 2003; De Sousa and De Sousa, 2004; Laaksonen *et al.*, 2007; Neto

*et al.*, 2007). We found that the number of days of DIS intake for patients who took it at least for one day revealed a high capacity for discriminating good prognosis, areas under the ROC curve for good prognostic being significant for all outcome variables and varying between 82 and 97% (93% for abstinence of heavy drinking). The 120-day cut-off point for patients who took DIS showed a high sensitivity and a relatively sufficient specificity of 97 and 68%, respectively, for avoiding a heavy drinking day (The cut-off of 120 days was based on work by Neto *et al.* (2007), which demonstrated the better effectiveness of DIS with at least 120 days of intake).

Taking DIS for less than 120 days proved to be one of the worst prognostic factors in this study, being associated with worse prognosis in all the outcome variables considered and having high risk ratios in multivariable analysis. We can speculate that cessation of DIS and consequent lack of effectiveness may relate to lack of adequate supervision and motivation of the co-responsible (Chick *et al.*, 1992; Hughes and Cook, 1997; Room *et al.*, 2005; Laaksonen *et al.*, 2007).

In respect of ACA, we found lack of effectiveness, as was already observed, for example, by Chick *et al.* (2000) and studies that found DIS superior to ACA (De Sousa and De Sousa, 2005; Laaksonen *et al.*, 2007). Unlike DIS, the number of days of ACA intake was not statistically associated with good prognosis, showing areas under the ROC curve of low magnitude and not statistically significant for patients with at least one day of intake. This suggests that greater number of days of ACA intake is not associated with better prognosis. One issue important to notice is that the median time of ACA intake was 90 days, about half of the time of DIS intake (179 days). This lack of motivation to persist with ACA medication could be one of the reasons why the ACA patients had worse prognosis. It is important to note that the preference between DIS and ACA was not dependent on patient severity: there were no significant differences between DIS patients and ACA patients (exclusive treatment groups) in respect of severity, including the number of years of heavy drinking, alcohol quantity in a typical day, median number of DSM-IV criteria and GGT level (results not shown). However, this was not a random double-blind comparative trial of DIS versus ACA and therefore, there might be unknown confounders—indeed perhaps more motivated patients will request DIS.

The number of visits made by the patient was important, the multivariable analysis showing relevant associations in four of the six outcome variables and areas under ROC curves showing significance related to visits attended. Indeed, attending more than half of the planned visits had a sensitivity of 92% and a specificity of 63% for absence of heavy drinking. (c.f. McKay and Weiss, 2001; McCrady and Epstein, 2004; Mann *et al.*, 2005; Terra *et al.*, 2008). Attending visits reinforces DIS adherence: the number of days of DIS taken correlated positively with the number of visits attended. The number of visits attended plus the number of days that DIS was taken improves sensitivity from 97% for DIS (at least 120 days taken) and 92% from visits attended (>50% of visits) to a sensitivity of 100% regarding absence of heavy drinking for patients with DIS prescription. This means that 100% of patients who avoided heavy relapse took DIS for >120 days and attended >50% of the planned visits (assuming that these patients had DIS prescription).



The greater number of phases in the consultation was also prognostic of good outcomes for four of the six outcome variables. (c.f. Neto *et al.*, 1997; David *et al.*, 1998; Neto *et al.*, 2008). We think that this is due to greater involvement of the co-responsible.

If we add the consultation type (more than two phases) to a patient who was already taking DIS for at least 120 days and >50% of the planned consultations, then we maintain the sensitivity of absence from heavy drinking at 100% but increase the specificity for 71% (assuming that these patients had DIS prescription). This means that 71% of heavy relapsed patients made fewer DIS (<120 days), with fewer visits (<4) and with fewer consultation phases (<2.5).

Regarding AA, this study did not support the association with good prognosis found by many others (e.g. Ellis and McClure, 1992; McKay and Weiss, 2001; Mello *et al.*, 2001; McCrady and Epstein, 2004; Room *et al.*, 2005; Ilgen *et al.*, 2007; Chong and Lopez, 2008; Terra *et al.*, 2008). However the low rate of AA attendance (18%) in our study does not lead to any conclusions.

Our sample comprised severely affected patients, similar to many alcohol-dependent patients in treatment. Our sample comprised 84% of males, with 41 years of median age, consuming a median of 192 g of alcohol during a median of 13 years of heavy drinking. If we consider the similar median values of several studies of alcohol-dependent persons in treatment, we get 74% of male patients with 43 years of median age, consuming a median of 193 g of alcohol during a median of 14 years of heavy drink (Ellis and McClure, 1992; McLellan *et al.*, 1994; Barrias *et al.*, 1997; Besson *et al.*, 1998; Chick *et al.*, 2000; Curran *et al.*, 2000; Rubio *et al.*, 2001; Guardia *et al.*, 2002; Willinger *et al.*, 2002; Johnson *et al.*, 2003; Staines *et al.*, 2003; Kiritzé-Topor *et al.*, 2004; De Sousa and De Sousa, 2004; Bottlender and Soyka, 2005a; Kiefer *et al.*, 2005; Kushner *et al.*, 2005; Mann *et al.*, 2005; Feeney *et al.*, 2006; Gordon *et al.*, 2006; Neves-Cardoso *et al.*, 2006; Sander and Jux, 2006; Walter *et al.*, 2006; Laaksonen *et al.*, 2007; Neto *et al.*, 2007; Nielsen *et al.*, 2007; Terra *et al.*, 2008). Thus, we believe our findings can be extrapolated to other patient populations.

Several limitations pertain. We had 28% lost to follow-up (who were classified as relapsed and for missing values of ARPQ at 6 months—about 36%—, classified as having at least one alcohol problem). Regarding external validity and generalization of results, one of the conditions for inclusion was the availability of a close person to inform or be co-responsible; this does not apply across the whole spectrum of alcohol-dependent patients.

Nevertheless, we believe that this study sheds light on some important features of treatment in a real environment.

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