TREATMENT

Effectiveness of Sequential Combined Treatment in Comparison with Treatment as Usual in Preventing Relapse in Alcohol Dependence

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Abstract — Aim: The aim of this study was to compare the effectiveness of the sequential combined treatment (SCT) and treatment as usual (TU) in relapse prevention in a sample of alcohol-dependent patients, during 180 days of outpatient treatment. Method: 209 alcohol-dependent patients who could attend with an informant adult were randomized to either TU or SCT. The primary outcome measure was time to first relapse, defined as the consumption of any amount of alcohol during the 180 days of follow-up. Secondary outcome measures included maximum duration of continuous abstinence (MDCA), cumulative abstinence duration (CAD), quality of life (ARFQ) and blood test markers of alcohol consumption. Results: The SCT approach was more effective than TU. The Kaplan–Meier abstinent proportion at the end of the 180 days was 78% for the SCT group and 59% for the TU group (P < 0.01). The mean time to first relapse was 150 days for SCT and 123 days for TU (P < 0.01). The relative risk reduction of relapse was 62% for SCT after adjustment in multiple Cox regression (P < 0.01). SCT had more MDCA (P < 0.05) and more CAD (P < 0.05). Therapy sessions lasted slightly longer for SCT than TU (mean 13 min versus 10 min). Conclusions: SCT can result in better outcomes than TU in the outpatient treatment of alcohol dependence.

INTRODUCTION

Portugal is among the world’s largest consumers of alcoholic beverages. In 2003, according to World Drink Trends (2005), it held 8th place, with a consumption of 9.6 l of ethanol per capita, behind countries such as Luxembourg, Czech Republic, Republic of Ireland, Germany, Spain and the United Kingdom.

The diseases caused by the excessive consumption of alcoholic beverages include the syndrome of dependence of alcohol (SDA), with an estimated prevalence in Portugal of 580,000 persons and the syndrome of abuse of alcohol (SAA), estimated at 746,000 persons (Gameiro, 1998).

The ambulatory treatment of SDA (defined following the American Psychiatric Association, 1994) in the Portuguese health service tends to follow a medical model based predominantly on an individual approach. The phase of detoxification is based mostly on the patient himself and is followed by medication for the maintenance of abstinence. This is the practice of usual treatment. Previous research into the treatment of SDA in Portugal was based on this approach and has shown very modest results (Barrias et al., 1997). In that randomized controlled study, the percentage of abstinent people at the end of 6 months of treatment was 45% of those who took acamprosate and 37% of those who took placebo, but this difference failed to achieve statistical significance. At the end of 1-year follow-up, acamprosate gave 39% of abstinence compared with 26% on the placebo group (P = 0.01). The mean time to the first relapse was 111 days for the acamprosate group and 55 days for the placebo group (P < 0.001).

Treatments with disulfiram exist in Portugal, but often without systematic supervision to assure adherence to the medication. Without this supervision, the treatment has not been shown to be effective (Fuller et al., 1986; Chick et al., 1992, 1999; Brewer et al., 2000). The only randomized and controlled studies that demonstrated that disulfiram was effective used it under supervision (Chick et al., 1992; Hughes and Cook, 1997; Brewer et al., 2000; Buri et al., 2007; Slattery et al., 2003; De Sousa and De Sousa, 2004, 2005; Laaksonen et al., 2007). De Sousa and De Sousa (2004) reported a time to first relapse of 103 days for the disulfiram group against 44 for the naltrexone group. In Laaksonen et al. (2007), these figures were 30 days for the disulfiram group, 16 for naltrexone and 11 for acamprosate.

In recent years, specialists in addiction’s treatment in Portugal have advanced some innovative developments. Independent of the community reinforcement approach (Azrin 1976, 1982; Smith et al., 2001), but with some similarities, they developed the sequential combined treatment (David and Neto, 1997; Neto et al., 1997; David et al., 1998), first for heroin addicts’ treatment with naltrexone, and then for alcoholics. With this method it has been possible to achieve encouraging rates of abstinence at the end of a year of SCT treatment of heroin addicts: 61% at the end of 6 months and 57% at the end of 1 year (Neto et al., 1997).

Expecting that the SCT approach works in a similar way as in other substance-addicted patients, the main hypothesis of this study is that the SCT approach can give better results than TU in the relapse prevention of alcoholic-dependent patients.

METHODS

This is an experimental randomized study comparing the effectiveness of TU and SCT, in the prevention of relapse of alcoholic patients, during a period of 180 days. It took place in two institutions dedicated to the treatment of alcoholic patients: the Centro Regional de Alcoologia do Sul (CRAS) and the Hospital de Nossa Senhora do Rosário (HNSR).
**Ethics**

The study protocol, written information for subjects and the consent form were approved by the Ethics committees of CRAS and HNSR.

**Participants**

The selection of the participants was made from the list of first consultations, in agreement with the inclusion criteria, to meet the criteria of diagnosis of SDA in accordance with DSM-IV, to be abstinent at least the last 24 h and without signs of withdrawal, to have a nominated informant person and to accept taking disulfiram if it is prescribed (through previous signature of a document with the detailed characteristics of this medicine, precautions and side effects).

Patients were excluded if they had psychiatric co-morbidity or severe physical disease; additive co-morbidity (except nicotine); not able to read or write; history of prior allergic reactions to disulfiram; decompensated hepatic disease, defined by one or more of the following: ascites, varical bleeding, jaundice and/or albumin <38 g/l, gamma glutamyl transferase (GGT) >600 u/l; alanine amino transferase (ALAT) >200 u/l; pregnant women or women of fertile age not practising contraception.

**Study design**

This is a randomized open trial with two arms, with patients receiving two treatment approaches (TU and SCT), and being followed in outpatient treatment at 4-week intervals for 6 months.

The inclusion of patients in the study and randomization scheme is shown in Fig. 1 (trial profile).

A computer-generated random numbers list was used to allocate to the two groups. This list was managed by the Nursing Department of CRAS, who attributed a number for each entrance in the study, and 209 patients with SDA (DSM IV) were randomized to two groups: SCT (n = 104) and TU (n = 105).

If detoxification had been needed, this took place before randomization.

From 841 cases consecutively registered at CRAS, 194 patients met inclusion criteria (23%). Recruitment at HNSR could not be based on a consecutive list, because this hospital did not have a specific service for the treatment of alcohol problems; from HNSR, 15 patients were recruited.

All patients and informants gave their written consent to take part in the study, including taking disulfiram if it was prescribed to the patient.


**Measures**

**Protocol of initial evaluation.** Evaluation of the psychosocial characteristics of the patients (Graffard 1956); pattern of alcohol consumption (obtained by questionnaire passed by the Assistant Researcher on the assessment interview); evaluation of the biological markers of heavy drinking: mean red cell volume (MCV), alanine amino transferase (ALAT) aspartate amino transferase (ASAT) and gamma glutamyl transferase (GGT). These tests were repeated at 180 days. For blood tests, normalization of the parameters was used (Sogliero-Gilbert et al., 1986), so that clinically normal values are in the range 0–1, and increased values are >1.

**Alcohol Related Problems Questionnaire (ARPQ) (Patience et al., 1997).** This questionnaire was used to evaluate problems related to alcohol during the past 6 months in the following areas: physical and mental health, work, family, social relations and the law. The version of the questionnaire we used (11 questions) employs a score from 11 to 22 points, a high score indicating few problems related to alcohol consumption. In this paper we converted the original ARPQ scores to the interval 0–1, indicating 1 the best quality of life level and 0 the worst.

This scale was used at the baseline and at 180 treatment days and inquires into the previous 180 days.

**TimeLine Follow-Back (TLFB) (Sobell and Sobell, 1992).** Using a monthly calendar as a guide, the patient supplies a retrospect of his drinking. From the TLFB, it is possible to determine the duration of total abstinence, the time until the first lapse to any drinking, the cumulative total of abstinent days, and to quantify the relapses and the amounts ingested per each day of relapse.

In recording alcohol consumption a ‘standard drink’ contained 10–12 g of ethanol.

The TLFB was documented by one of two independent assessors (ignorant to the treatment group), with previous training in the use of this method, every 15 days by telephone interview with the patient and the informant person. In the case of divergence of information, the most pessimistic version was chosen.

The TLFB interview documented the number of days of observed consumption of disulfiram, attendance at AA and at the clinic.

If, during the follow-up (180 days), the physician considered that brief readmission to hospital was needed, this could be proposed, but the days during which the patient was in hospital were not included in the denominator for calculating the percentage of abstinent days.
A research assistant chronometered the time spent on each one of the five consultations with the doctor, without the previous knowledge of the participant doctors. This approach was important, in order to compare the mean time of SCT and TU consultations. Patients who missed an appointment were sent one letter for another appointment by the research assistant.

**Modalities of treatment**

*Treatment as usual—TU.* TU corresponds to the customary biomedical approach in Portugal for prevention of relapse of patients with SDA, with a psychiatrist as the sole therapist, and typically consisting of mental state assessment, review of the onset, pattern of drinking and comorbidities. A medication protocol adjusted to each patient is typically proposed. In general, each consultation includes encouragement to abstain, with an explanation of the nature of alcohol dependence. Specifically, it implies:

- An approach centred in the patient, who takes all the medication by himself and without supervision. There is not a systematic role for a ‘co-responsible’. Involving the family is, therefore, optional, at the family’s or the doctor’s request.
- Each consultation has one or two phases. Usually the patient is alone, less often with a family member (consultation consisting of one phase). If a family member attends, typically the patient is initially seen alone, with occasionally a second phase with this family member and the patient, at the request of the doctor, the patient or the family member.
- Psychosocial characteristics and drinking patterns are assessed through questioning the patient and later the family member if considered necessary.
- Compliance to treatment is discussed.
- Patients are advised to go to Alcoholics Anonymous (AA).
- Complete abstinence is encouraged; prescription of supervised disulfiram is uncommon.

**Sequential combined treatment—SCT.** SCT is a combined family, normative and stepped approach that seeks to maximize the family and social reinforcement for abstinence.

It always involves another adult person, significant in the life of the alcoholic patient, in affective and logistic terms, preferably living with him. The patient voluntarily puts this person into the co-responsible role for his treatment. (In this study, the SCT informant person had her role upgraded to co-responsible.) Each patient is followed-up by only one therapist, usually a physician, who counsels and prescribes medication, in consultations up to 20 min. The interval between the consultations is not fixed.

‘Sequential’ means a sequence of therapeutic strategies, starting with abstinence, family relations and the professional area (for example to look for a job), all with the aim of helping the patient to find a productive and independent style of life.

‘Combined’ means that each consultation offers at the same time individual and family counselling, combining the psychopharmacologic, psychotherapeutic and family approach, the premise being that the patient with SDA suffers but also makes the system around him suffer, so that treatment intervenes in the system as well.

Specifically it implies:

- All consultations are attended and all medications, for detoxification and disulfiram, are supervised by the co-responsible.
- SCT typically consists of consultations in four phases of around 5 min each (longer on the first consultation), with an experienced physician, taking about 20 min in total: First phase: with the patient and the co-responsible, to gather all the information possible. Second phase: with the patient only, to gather more information and to see what is indicated on attitudes and medication. Third phase: with the co-responsible only, to gather more information and to talk more privately about the patient’s characteristics, intervention of the co-responsible and chances of recovery. Fourth phase: with the patient and the co-responsible again, to prescribe, explain the prescriptions and have the agreement of the whole system.
- In follow-up, the number of phases of each consultation can be reduced.
- Information revealed by the different parts is not necessarily shared; the therapist does not ‘betray’ the patient, saying one thing when he is present and something different when he is absent.
- Respect and appreciation are shown, both for the patient and for the co-responsible, and appreciation for his efforts to remain abstinent. The therapist requests the patient’s permission for the ‘phasing’ of the consultation. Relapse is not viewed as immoral or shaming.
- The family approach of SCT is ‘Firm Love’, as practised by some 12-step movements, but without ‘hardness’; reciprocal affectionate rewards between the patient and the co-responsible and family are encouraged.
- Patients are advised to attend AA meetings.
- Complete abstinence is encouraged and prescription of supervised disulfiram is usual.

**The therapists**

The eight therapists in this study were all medical doctors with the experience of treating alcohol patients (six at CRAS and two at HNSR), representative of two groups, four who practised TU and four who practised SCT, each group working consonant with their best clinical practice. They were chosen, according to their practice, to give only one type of treatment, either TU or SCT.

SCT doctors were slightly older than TU doctors (mean age 55 versus 54) and had slightly more years of experience (mean 25 years versus 23).

**Outcome measures**

*Primary outcome variable.* Time to first relapse was considered as the consumption of any quantity of alcohol. Complete abstinence throughout the 180 days was termed ‘abstinence’.

*Secondary outcome variables.*

(a) Maximum duration of continuous abstinence (MDCA), in days.
Table 1. Comparison between the groups at baseline

<table>
<thead>
<tr>
<th></th>
<th>TU (n = 105)</th>
<th>SCT (n = 104)</th>
<th>Total (n = 209)</th>
<th>Value of the test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender n(%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>89 (85%)</td>
<td>87 (84%)</td>
<td>176 (84%)</td>
<td><strong>χ² 0.048</strong></td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>16 (15%)</td>
<td>17 (16%)</td>
<td>33 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [mean (Standard deviation)]</td>
<td>42 (8)</td>
<td>41 (8.5)</td>
<td>41.6 (8.2)</td>
<td><strong>T 1.038</strong></td>
<td>ns</td>
</tr>
<tr>
<td>Years at school [mean (Standard deviation)]</td>
<td>6.9 (3)</td>
<td>7.6 (4)</td>
<td>7 (3.3)</td>
<td><strong>T = 1.474</strong></td>
<td>ns</td>
</tr>
<tr>
<td>Professional situation, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular job</td>
<td>48 (46%)</td>
<td>53 (51%)</td>
<td>101 (41%)</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Irregular job</td>
<td>20 (19%)</td>
<td>13 (13%)</td>
<td>33 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>34 (32%)</td>
<td>37 (36%)</td>
<td>71 (34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
<td>4 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social class (Graffard), n(%)</td>
<td></td>
<td></td>
<td></td>
<td><strong>χ² 5.428</strong></td>
<td>ns</td>
</tr>
<tr>
<td>Class II (medium–high)</td>
<td>7 (7%)</td>
<td>14 (14%)</td>
<td>21 (10%)</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Class II (medium)</td>
<td>27 (26%)</td>
<td>33 (32%)</td>
<td>60 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III (medium–low)</td>
<td>53 (51%)</td>
<td>38 (37%)</td>
<td>91 (44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IV (low)</td>
<td>18 (17%)</td>
<td>19 (18%)</td>
<td>37 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective-sexual relation with cohabitation, n(%)</td>
<td></td>
<td></td>
<td></td>
<td><strong>χ² 4.147</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>65 (62%)</td>
<td>78 (75%)</td>
<td>143 (68%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40 (38%)</td>
<td>26 (25%)</td>
<td>66 (32%)</td>
<td></td>
<td>0.042</td>
</tr>
<tr>
<td>Informant (or co-responsible), n(%)</td>
<td></td>
<td></td>
<td></td>
<td><strong>χ² 4.041</strong></td>
<td>ns</td>
</tr>
<tr>
<td>Spouse</td>
<td>61 (58%)</td>
<td>67 (64%)</td>
<td>128 (68%)</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Parents</td>
<td>21 (20%)</td>
<td>20 (19%)</td>
<td>41 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other family members/friends</td>
<td>21 (20%)</td>
<td>12 (12%)</td>
<td>33 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult children</td>
<td>2 (2%)</td>
<td>5 (5%)</td>
<td>7 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of excessive consumption of alcohol [mean (SD)]</td>
<td>13.5 (8)</td>
<td>13.3 (7.4)</td>
<td>13.4 (7.7)</td>
<td><strong>T 0.168</strong></td>
<td>ns</td>
</tr>
<tr>
<td>Total (grams) at a typical day of consumption [mean (SD)]</td>
<td>209 (115.7)</td>
<td>241 (149.7)</td>
<td>225 (134)</td>
<td><strong>T = 1.706</strong></td>
<td>ns</td>
</tr>
<tr>
<td>Time (days) of abstinence [mean (SD)]</td>
<td>22 (31.9)</td>
<td>21 (29.6)</td>
<td>21 (31)</td>
<td><strong>T 0.287</strong></td>
<td>ns</td>
</tr>
<tr>
<td>Pattern of consumption, n(%)</td>
<td></td>
<td></td>
<td></td>
<td><strong>χ² 0.607</strong></td>
<td>ns</td>
</tr>
<tr>
<td>Diary</td>
<td>96 (91%)</td>
<td>94 (90%)</td>
<td>190 (91%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Of weekends</td>
<td>6 (6%)</td>
<td>5 (5%)</td>
<td>11 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodic</td>
<td>3 (3%)</td>
<td>5 (5%)</td>
<td>8 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of drugs in the past, n(%)</td>
<td></td>
<td></td>
<td></td>
<td><strong>χ²</strong></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>10 (10%)</td>
<td>12 (12%)</td>
<td>22 (11%)</td>
<td></td>
<td>0.225</td>
</tr>
<tr>
<td>Cocaine</td>
<td>8 (8%)</td>
<td>13 (13%)</td>
<td>21 (10%)</td>
<td></td>
<td>1.337</td>
</tr>
<tr>
<td>Cannabis</td>
<td>9 (9%)</td>
<td>23 (22%)</td>
<td>32 (15%)</td>
<td></td>
<td>7.392</td>
</tr>
<tr>
<td>BZD not prescribed</td>
<td>10 (10%)</td>
<td>13 (13%)</td>
<td>23 (11%)</td>
<td></td>
<td>0.473</td>
</tr>
</tbody>
</table>

(b) Cumulative abstinence duration (CAD), described as the total number of days of abstinence.
(c) Sum of days of relapse (SDR).
(d) Maximum duration (days) of each relapse (MDR).
(e) Mean of the number of drinks ingested at a drinking day (MD), described as the sum of the total of drinks ingested divided by the total number of days of relapse.
(f) Change in ARPQ, MCV, ALAT, ASAT, GGT, between baseline and 180 days, computed within each individual.

**Medication**

In both modalities of treatment, doctors were instructed to use medicines, when indicated, from this list: acamprosate; disulfiram in doses of 125 or 250 mg/day, permitted to be doubled or tripled doses on Fridays if the patient was absent during weekend; anti-depressants (sertraline, venlafaxine, mirtazapine), buspirone as anxiolytic, diazepam and tiapride should alcohol detoxification be indicated during any relapses.

**Statistical analysis**

A comparative analysis was made of the two groups with respect to baseline characteristics and outcome. The chi-square and Fisher’s exact test were used for categorical variables (χ²), and Student’s t (T) and Mann–Whitney (MW) tests for the numerical variables (the MW test was used when normality does not seem to hold). Through survival analysis (Kaplan–Meier), the two groups were compared relative to the number of days up to the first relapse and the abstainers’ ratio until the end of 180 days (the Kaplan–Meier method takes account of dropouts as censored data).

In other statistical analysis, loss to follow-up was regarded as relapse (intention to treat method—Gillings and Koch 1991).

Cox regression analysis was performed for adjustment of possible confounding variables. An estimate was made of the relative risk (Hazard ratio) of SCT versus TU, as well as its 95% confidence interval, estimated through the Cox regression analysis.

All the statistical analyses were done in SPSS version 14, with the statistical methodology of Altman (1991) and Aguiar (2007); any inferential analytic result associated with a P value of <0.05 was considered statistically significant.

**RESULTS**

Table 1 shows that the groups did not differ in baseline characteristics, except in the variables affective-sexual relation for which the SCT group had more patients with a steady cohabitation (75% in comparison with the TU group 62%; P < 0.05) and previous consumption of cannabis (SCT group 22% versus TU group 9%; P < 0.01).
The analysis of the effect of the treatment was adjusted for these potentially confounding variables. The informant ('co-responsible' in SCT) in the two groups was usually the spouse. Patients reported a problem with alcohol for the past 13 years on average, with a pattern mainly of daily consumption and with a mean of 209 g (TU) and 241 g (SCT) of ethanol per typical day of drinking. At baseline, patients had been abstinent for a mean of 22 (TU) and 21 (SCT) days.

Regarding the parameters to be used as outcome measures there was no difference between the groups at baseline. Among the secondary outcome measures, there were no statistically meaningful differences in ARPQ, VGM, ALAT, ASAT and GGT at baseline (the average adjusted values were VGM 0.98 fl, ALAT 1.23, ASAT 1.17 and GGT 2.4, values which suggest some level of severity of dependence, i.e. above the superior limit of the normal in ALAT and ASAT and very increased values of GGT); ARPQ was on average 0.52, showing that in general patients had a moderate level of problems connected with alcohol.

**Treatment received.** More patients completed treatment in SCT than in TU (without statistical significance). Patients had a mean of four consultations of follow-up during the 180 days of study, without differences between the groups. For SCT, the co-responsible was present at 99% of the consultations, compared to 69% for TU. Referring to the phases of the consultations, TU consisted of consultations mainly in one phase. For SCT, consultations were mainly in three and four phases. A greater percentage of patients attended meetings of AA in the SCT group than in the TU group. Most of all these differences were statistically significant (Table 2).

Concerning the duration of the consultations, SCT sessions lasted a mean of 13 min, with a maximum of 30 min in a consultation of four phases; TU consultations lasted a mean of 10 min, with a maximum of 16 min. We remind readers that the assessments made by the auxiliary researcher helped to shorten the duration of the first medical consultation in both groups.

Regarding consumption of relapse-prevention medications, we compared the numbers of patients who we knew had effectively taken disulfiram. Disulfiram was effectively taken by 88 (85%) of the patients of the SCT group versus 60 (57%) of the patients of the TU group ($P < 0.001$). The mean number of days of effectively taking disulfiram was greater in the SCT group (151 days) than in the TU group (127 days) ($P < 0.001$). More patients in the TU group took acamprosate 22% versus 7% ($P < 0.05$), with more mean days of consumption of this medication (97 versus 45; $P < 0.05$).

Other medicines different from disulfiram were taken by 75% of the TU group, versus 44% of the SCT group ($P < 0.001$). The TU group took significantly more tiapride and buspirone. There was no significant difference between the two groups regarding the numbers of patients who took anti-depressants and benzodiazepines. Regarding buspirone, SCT patients took less, but with a longer time of intake. A mean of two medicines were taken by each patient of TU compared to 1.5 medicines per patient in the SCT group ($P < 0.05$).

### Table 2. Comparison between the groups face to the characteristics of the treatments

<table>
<thead>
<tr>
<th>Variables</th>
<th>TU</th>
<th>SCT</th>
<th>Test</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed treatment, n (%) $n = 209$</td>
<td>61 (58%)</td>
<td>72 (69%)</td>
<td>$\chi^2 2.8$</td>
<td>ns</td>
</tr>
<tr>
<td>Frequent consultations [mean (SD)]</td>
<td>3.7 (1.6)</td>
<td>4 (1.4)</td>
<td>T $-1.375$</td>
<td>ns</td>
</tr>
<tr>
<td>Percentage of presences of the informant (or co-responsible) in the consultations [mean (SD)]</td>
<td>69 (31)</td>
<td>99 (19)</td>
<td>T $-5.701$</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Mean of the phases of the consultations [mean (SD)]</td>
<td>1.2 (0.34)</td>
<td>3.1 (0.88)</td>
<td>T $-20.050$</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Frequent meetings of AA, n (%)</td>
<td>11 (11%)</td>
<td>27 (26%)</td>
<td>$\chi^2 8.422$</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Disulfiram taken, n (%) $n = 148$</td>
<td>60 (57%)</td>
<td>88 (85%)</td>
<td>$\chi^2 9.1$</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>In this group, days disulfiram taken [mean (SD)]</td>
<td>127 (57)</td>
<td>151 (49)</td>
<td>T $-2.779$</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Other medicines taken, n (%) $n = 125$</td>
<td>79 (75%)</td>
<td>46 (44%)</td>
<td>$\chi^2 20.898$</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Antidepressants taken, n (%) $n = 56$</td>
<td>32 (31%)</td>
<td>24 (23%)</td>
<td>$\chi^2 1.46$</td>
<td>ns</td>
</tr>
<tr>
<td>In this group, days antidepressants taken [mean (SD)]</td>
<td>130 (59)</td>
<td>132 (59)</td>
<td>T $-0.106$</td>
<td>ns</td>
</tr>
<tr>
<td>Acamprosate taken, n (%) $n = 30$</td>
<td>23 (22%)</td>
<td>7 (7%)</td>
<td>$\chi^2 9.79$</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>In this group, days acamprosate taken [mean (SD)]</td>
<td>97 (53)</td>
<td>45 (24.8)</td>
<td>T $3.579$</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Benzodiazepines taken n(%) $n = 44$</td>
<td>27 (26%)</td>
<td>17 (16%)</td>
<td>$\chi^2 2.76$</td>
<td>ns</td>
</tr>
<tr>
<td>In this group, days benzodiazepines were taken [mean (SD)]</td>
<td>66 (52)</td>
<td>32 (37)</td>
<td>T $2.924$</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Tiapride taken n(%) $n = 26$</td>
<td>21 (20%)</td>
<td>5 (5%)</td>
<td>$\chi^2 11.07$</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>In this group, days tiapride taken [mean (SD)]</td>
<td>83 (61)</td>
<td>62 (69)</td>
<td>T $-0.890$</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Buspirone taken n(%) $n = 16$</td>
<td>12 (11%)</td>
<td>4 (4%)</td>
<td>$\chi^2 4.25$</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>In this group, days buspirone taken [mean (SD)]</td>
<td>66 (36)</td>
<td>141 (52)</td>
<td>T $-2.314$</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Number of medicines taken except disulfiram [mean (SD)]</td>
<td>2 (1)</td>
<td>1.5 (0.7)</td>
<td>T $-2.532$</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Number of medicines taken including disulfiram [mean (SD)]</td>
<td>3 (1)</td>
<td>2.5 (0.7)</td>
<td>T $-2.532$</td>
<td>$P &lt; 0.05$</td>
</tr>
</tbody>
</table>
If we include disulfiram we see that, in spite of the bigger uptake of this medicine in the SCT group, patients of TU took a mean of 2.97 medicines versus SCT, among whom patients took a mean of 2.52 medicines. The difference of medication taken is still significant ($P < 0.05$).

**Outcome**

The Kaplan–Meier analysis was used to compare the two groups with respect to the time of the first relapse and the proportion of abstainers during the 180 days.

The Kaplan–Meier proportion of abstainers during the 180 days was greater for the SCT group, than the TU group, as well as at 30, 60, 90 and 120 days. By the end of 180 days, 78% of SCT patients were abstinent compared to 59% of TU patients. At days T30, T60, T90 and T120 the abstainers’ proportion in TU was 79%, 71%, 65% and 64%, and in SCT it was 89%, 87%, 83, and 79%, respectively. The biggest percentage of relapses happened in the first 90 days of treatment, with a significant difference was seen between the two abstinent proportion in both groups.

Through the log rank (Mantel–Cox) test, a statistically significant difference was seen between the two abstinent proportion curves ($P < 0.01$). The mean time to first relapse was 123 days for the TU group and 150 days for the SCT group (Fig. 2).

**Adjusted analysis for potential confounders**

Because the groups were unbalanced for two baseline variables (affective-sexual relation with cohabitation and previous use of cannabis), we applied a multiple Cox regression model adjusted for these variables to measure the effect of SCT compared with TU.

When these variables were included in the Cox regression model a relative risk (Hazard ratio) for SCT versus TU of $RR = 0.38$ ($P < 0.01$) was obtained (confidence interval of 95% between 0.21 and 0.69), which allows the conclusion that the relative risk reduction of relapse is around 62% (0.38–1). Given that the not-adjusted Hazard ratio is 0.48, we can be confident that we have shown a true effect.

In this way it can be inferred that, for each patient who relapses in the SCT group, there are between two and three patients relapsing in TU.

Because more patients in SCT took disulfiram than in TU, we repeated the analysis within all those who took at least one dose of disulfiram ($n = 148$). The protective effect of SCT was still present and statistically significant ($P < 0.001$) (multiple Cox regression model adjusted for affective sexual relation and previous use of cannabis). This suggests that the effectiveness of SCT is not only connected with using disulfiram.

**Secondary variables of efficacy (Table 3)**

The SCT group achieved a longer period of continuous abstinence than the TU group (130 days versus 111 days; $P < 0.05$). Of the total treatment time in study, SCT patients were more often abstinent than TU patients (138 versus 125 days, $P < 0.05$). The SCT group had fewer days of relapse in comparison with the TU group (13 days versus 26 days, without statistical significance). The maximum duration of the periods of relapse was longer in TU than in SCT (18 versus 6 days, $P < 0.05$). The ingested quantities of alcohol in each relapse were 6 units for the TU group and 4 units for the SCT group ($P < 0.05$).

The change in ARPQ at 180 days of treatment (mean 0.42 in the TU group and 0.46 in the SCT group) indicates improvements in various areas of life in both groups (advantage to SCT not statistically significant).

The blood test parameters improved in the two groups, and this is expected due to the great proportion of abstainers contained in the sample that remained in the study at the end of 6 months. As explained in the Method section, normalized values were used. No statistically significant differences were found between the groups.

**Characteristics of treatment associated with abstinence**

Abstinence was associated with a greater number of days of taking disulfiram (172 days and 124 days, respectively, for abstinent and relapse groups, $P < 0.001$). The mean number of phases of each consultation was greater for abstinent than relapsed patients, respectively, 2.5 and 1.8 ($P < 0.001$).

The presence of the informant (or co-responsible) in the consultation was not statistically associated with abstinence, though there is a tendency for a greater percentage of his/her presence in the group of the abstainers.

Table 3. Secondary variables of efficacy

<table>
<thead>
<tr>
<th>Variables</th>
<th>TU Average in days (SD)</th>
<th>SCT Average in days (SD)</th>
<th>MW test</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum duration of continuous abstinence (MDCA)</td>
<td>(n = 105) 111 (70)</td>
<td>(n = 104)130 (67)</td>
<td>−2.204</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Cumulative abstinence duration (CAD)</td>
<td>(n = 105) 125 (68)</td>
<td>(n = 104)138 (65)</td>
<td>−2.186</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>For patients who relapsed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum of days of relapse (SDR)</td>
<td>(n = 37) 26 (33)</td>
<td>(n = 20) 13 (18)</td>
<td>−1.722</td>
<td>ns</td>
</tr>
<tr>
<td>Maximum duration of each relapse (MDR)</td>
<td>(n = 38) 18 (26)</td>
<td>(n = 21) 6 (11)</td>
<td>−2.842</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>Mean of the number of drinks ingested by drinking day (MD)</td>
<td>(n = 30) 6 (3)</td>
<td>(n = 20) 4 (4)</td>
<td>−2.457</td>
<td>$P &lt; 0.05$</td>
</tr>
</tbody>
</table>

Fig. 2. The curve of Kaplan–Meier for the two groups ($P < 0.01$).
DISCUSSION

Treatment integrity
Despite the fact that it was impossible to control what therapists really did in the treatment sessions, besides their expressed commitment to TU or SCT practices, we have an indicator of some fidelity to the respective approaches. The involvement of the informants (or co-responsible) is related to the phases of the consultations (to three or to four phases). In the theoretical optimal sense we expected that SCT had four phases and TU two phases. We found in our study that SCT had a mean of 3.1 phases and TU 1.2 phases, and these empirical values are with some proximity to the expected values, maintaining relatively the ratio 2:1 between the phases of the two approaches. This is a good indication of internal validity.

Efficacy
The results suggest overall better outcomes for patients in this study than in some similar outcome studies. The median time of survival up to the first relapse was 150 days for the SCT group and 123 days for the TU group. Barrias et al. (1997) in a Portuguese study reported a median time to first relapse of 111 days for the group allocated to acamprosate and 55 days for the placebo group. In De Sousa and De Sousa (2004), these figures were of 103 days for the disulfiram group and 44 days for naltrexone. In Laaksonen et al. (2007), these figures were of 30 days for the disulfiram group, 16 for the naltrexone and 11 for acamprosate. Maybe our better results were due to better characteristics of the sample (patients with family and who agreed in advance to take disulfiram if it was offered) but perhaps also to a clear emphasis of abstinence as an objective and to the presence of more family approach (albeit less structured in TU and more structured in SCT). In TU the informant (or co-responsible) was present at 69% of consultations versus 99% in SCT. This number (69%) suggests that TU in CRAS turns out to be somewhat contaminated with the active treatment agent.

The fact that the patients in the SCT group took less medication, or TU medical doctors are probably a factor in maintaining abstinence.

Characteristics of SCT treatment
The SCT characteristics that are connected with the achieved success have been essentially the taking of disulfiram and the phases of the consultations. The presence of the co-responsible in consultations is more frequent in SCT patients, and this is probably a factor in maintaining abstinence.

Besides the presence of the relative in the consultation, it seems that factors contributing to success may be the underlying logic of the joining/separation of the consultation (patient and co-responsible), ‘firm love’ and the normativity.

This study also demonstrated the importance of the supervised consumption of disulfiram. The fact that from 106 patients of the study who had already had previous treatments, only 12 had previous experience with this medication, displays the paucity of its use by Portuguese addiction specialists.

Limitations of the study
To what extent is SCT more like a mediator than a treatment agent that improves compliance to the medication, which, in turn, is the active treatment agent?

One of the aspects of the effectiveness of the SCT, which, as stated before, is a package of clinical attitudes and treatments, is the capacity of motivating the patients for the treatment and consequent maintenance of the abstinence.

One of the best indicators of the motivation for the treatment is the fact of the patient of having completed 6 months of treatment, which was 69% for the SCT group, against 58% of TU. Another important indicator of the level of the motivation is the number of attended consultations, which was slightly superior for SCT. As these differences were not statistically significant, only further studies may clarify these aspects.

Even though the therapists in the two treatment types had similar lengths of experience, it is possible that some other therapist characteristics biased the result. We did not attempt to measure therapist characteristics. As stated, therapists only gave either TU or SCT. Because one therapist was associated with a higher than average frequency of relapse, compared with the overall results, we repeated the analysis excluding that doctor’s cases, and the advantage of SCT remained.

This research was done with a highly selected sample, who had previously agreed to take disulfiram if it was prescribed. A study that removed this condition for participation would probably be more representative of typical clinical populations.

The fact that the patients in the SCT group took less medication than TU patients may signify one of three things: either they were psychologically healthier than TU patients, or SCT in general requires less medication, or TU medical doctors are used to prescribe more for minor problems that can be dealt with simple advice or counseling. Since there was a randomization of treatments, we should expect some psychological homogeneity of two groups of treatment, but because no psychological tests were done at the beginning, we cannot directly answer to confirm this. Thus a limitation of this study was the absence of psychological tests at entry, to evaluate the homogeneity of the samples in relation to mental vulnerability and consequent

There were 26% of SCT patients and 11% of TU patients who attended AA, but it was not possible to demonstrate a statistically significant effect of AA attendance on outcome.
necessity for psychiatric medication. This happened because we considered this study as predominantly directed towards the evaluation of alcohol consumption. However, the discrepancy of the quantity of medication in each group of treatment suggests that subsequent studies should analyze this factor.

Subsequent research should examine which are the more effective components of SCT: it might be the insistence on the presence of a co-responsible, or the division of the consultation in phases, or the general attitude of firm love, or the emphasis on the prescription of disulfiram under supervision, or perhaps another component still yet to discover.

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REFERENCES


