comunicação breve

Efficacy of acamprosate in the treatment of alcohol-dependent outpatients

Eficácia do acamprosato no tratamento ambulatorial de dependentes de álcool

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Abstract **Objective:** To evaluate the efficacy and security of acamprosate in the treatment of 75 men, aged 18 to 59 years, with diagnosis of alcohol dependence according to the ICD-10.
Methods: Double-blind, placebo-controlled study, 24-week long. After a one-week detoxification period, patients were randomly divided in two groups: the first group received acamprosate (six tablets of 333 mg/d for 12 weeks) and the second group received placebo (six tablets for 12 weeks). After the first 12 weeks, patients continued the follow-up for further 12 weeks without medication.
Results: Patients who were receiving acamprosate showed significantly higher continuous abstinence time within the 24 weeks of treatment compared with patients who were assigned to placebo treatment (p=.017). Twenty-five percent of patients who were receiving acamprosate and 20% of the placebo-treated patients dropped out. Few side-effects were reported in both groups.
Conclusion: Acamprosate proved to be safe and effective in treating alcohol-dependent patients and to maintain the abstinence during 24 weeks.

Keywords Alcoholism. Pharmacological treatment. Acamprosate.

Resumo **Objetivo:** Avaliar a eficácia e a segurança do acamprosato no tratamento ambulatorial de setenta e cinco pacientes do sexo masculino, com idade entre 18 e 59 anos, com diagnóstico de dependência de álcool pelo CID-10.
Métodos: Trata-se de estudo duplo-cego controlado e randomizado, com duração de 24 semanas. Após um período de desintoxicação de 1 semana, os pacientes foram divididos aleatoriamente em dois grupos: o primeiro grupo recebeu acamprosato (seis comprimidos de 333 mg por dia durante 12 semanas), e o segundo recebeu placebo (seis comprimidos por dia durante 12 semanas). Após as primeiras 12 semanas, os pacientes continuaram o tratamento por mais 12 semanas sem uso de medicação.
Resultados: Os pacientes que receberam acamprosato mostraram maior tempo de abstinência contínua ao longo das 24 semanas de tratamento quando comparados aos que receberam placebo (p=0,017). 25% dos pacientes que estavam recebendo acamprosato e 20% dos pacientes que estavam recebendo placebo abandonaram o tratamento. Poucos efeitos colaterais foram registrados em ambos os grupos.
Conclusão: O acamprosato mostrou ser seguro e eficaz no tratamento de pacientes dependentes de álcool e na manutenção da abstinência durante 24 semanas.

Descritores Alcoolismo. Tratamento farmacológico. Acamprosato.

*Study performed in the Interdisciplinary Study Group of Alcohol and Drugs of the Psychiatric Institute of the Clinical Hospital of the Medical School of the University of São Paulo (GREA-IPq-HCFMUSP)

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Introduction

The treatment of the syndrome of alcohol dependence can be conducted several ways being psychotherapies, mutual supporting groups, psychopharmacological treatment, psychosocial support and inpatient treatment the main ones.[1]

Current studies in neurosciences are implying new neurotransmission systems, such as those involved in mesocorticolimbic structures, in the pathophysiology of alcoholism.[2] Therefore, the development of new pharmacological models in the treatment of alcoholism has become a field of increasing interest among researchers all over the world.[3]

Regarding the pharmacological treatment, dissulfiram, naltrexone and acamprosate have shown efficacy in several clinical trials involving placebo. The most recently investigated drug is acamprosate, which has been used in the treatment of the syndrome of alcohol dependence for more than one decade in several countries.[4,5] This drug, which has an analogous structure to GABA (aminobutyric acid) is an agent which inhibits the glutamatergic excitatory activity, acting, probably, on a subclass of glutamate receptor (NMDA), especially when there is hyperactivity of these receptors. Acamprosate has been considered as a partial co-agonist of the NMDA receptor.[6,7]

These actions of acamprosate are compatible with the hypothesis that this medication suppresses the hyperactivity associated to high levels of excitation of the glutamate receptor during alcohol withdrawal in dependent patients. Therefore, this medication reduces the toxicity induced by glutamate.[8]

It seems that acamprosate also reduces calcium reuptake induced by neuronal glutamate, suppresses ethanol-conditioned responses in dependent animals, even in those with prolonged abstinence, reduces the aversive effects of alcohol withdrawal, inhibits the cerebral hyperexcitability induced by glutamate and inhibits the genic expression of c-fos.[9] It seems to have also a serotonergic and beta-adrenergic action.[10]

It has been suggested that acamprosate provokes reduction in craving; however, the neural mechanisms involved in this finding remain obscure.[11,12] Activity over the gabaergic system has been described, involving mainly subcortical pathways.[13] Daoust et al[14] described, in an experimental study, that acamprosate improves the reuptake of GABA in the thalamus and in the hippocampus of alcoholized mice.

The recommended dose of acamprosate is 1,3 g/day for people below 60 kg and 2,0 g/day for patients weighing 60 kg or more.

This study aimed to assess the therapeutic efficacy and safeness of acamprosate versus placebo, during a three-month period using the medication, with further three-month follow-up.

Methods

This study was developed by the Interdisciplinary Study Group of Alcohol and Drugs of the Psychiatric Institute of the Clinical Hospital of the Medical School of the University of São Paulo (GREA-IPq-HCFMUSP).

It was a double-blind randomized study, approved by the Ethical and Research Committee for the Analysis of Research Projects (CAPPesq).

The initial sample was composed by 75 patients who were randomically distributed in two groups.

A group of 40 patients received acamprosate for a 12-week period, from the entrance of the patient in ambulatorial follow-up onwards. Other group of 35 patients received placebo during the first 12 weeks of the study, being assessed in the same way as the first group. After this 12-week period, in which patients received the medications, treatment was continued for more 12 weeks, according to the usual procedures of GREA (behavioral orientation, clinical assessment and incentive to the participation in the group of Anonymous Alcoholic) to which patients were submitted during the whole study. Of note, the participation in the Anonymous Alcoholic groups was not a mandatory condition in the study.

All patients received the diagnosis of alcohol dependence syndrome, according to the criteria of the Classification of Mental and Behavioral Disorders of the ICD-10.[15]

Medication, whether placebo or acamprosate, was given to patients in identical tablets since the first ambulatory consultation. The patient was instructed to take two tablets in the morning, two at noon and two at night, always before meals.

Patients were assessed regarding the period of continuous abstinence, laboratory exams to assess hepatic function were performed and the UKU side effect rating scale was administered.[16]

Each patient was clinically assessed during 10 consultations.

Inclusion and exclusion criteria

1. Inclusion criteria: male patients entering treatment in GREA, with a diagnosis of alcohol dependence according to the ICD-10 criteria, aged 18 to 59 years, weighting more than 60 Kg.
2. Exclusion *criteria*: patients with clinical and psychiatric pathologies who needed treatment and previous psychotic pictures, as well as use of psychiatric and non-psychiatric medications.

Statistical analysis

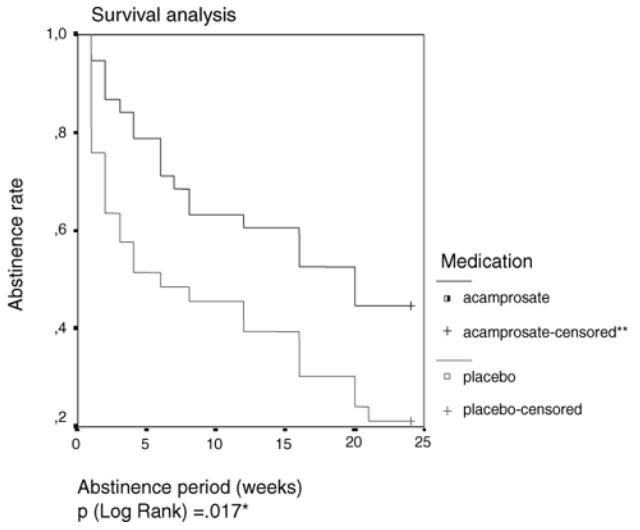
Data were processed with the SPSS 9.0 and STATA statistical programs.

In order to assess the period of continuous abstinence, i.e., the time period since the patient entered the study up to the first relapse, we used the Survival Analysis (Kaplan Meier). The Intention-to-Treat principle (ITT) was adopted, that is, any patient who, after the randomization, had received at least one dose of the medication being studied is eligible for statistical analysis. In this case, dropouts were considered as relapses. The significance level adopted was 5%.

Survival analysis is a method which can be used when there is interest to focus in the time until the occurrence of a specific event.

In clinical trials, the survival time refers to the time period between a specified procedure and death, or between the procedure and the appearance of a specific symptom or between the procedure and the relapse after the remission of a disease.[17]

To assess the difference between the reasons for study dropout in both groups we used the chi-square test. For the assess-



*p<.05
**Suspended assessment time (24-week study)

Figure - Survival analysis (Acamprosate Group and Placebo Group) duration rate of continuous abstinence in patients with alcohol dependence syndrome receiving acamprosate or placebo.

ment of the difference between the number of cases of follow-up dropout in both groups and the rate of side-effects we used Fisher's Exact Test.

Results

The initial sample included 75 patients (new cases), who were seen from December 2000 to February 2002. Seventeen patients did not complete the 24-week study (10 in the acamprosate group and seven in the placebo group) (p=.783, Fisher's Exact Test), as they dropped out the follow-up, what corresponded to 23% of the patients screened for the study.

The Survival Analysis can be observed in Figure, based on the continuous abstinence time, denoting a statistically significant difference between survival curves of acamprosate and placebo. According to this principle, any patient who interrupted the treatment (dropout) before the established time was considered as a 'failure', as well as relapses.

Four patients were excluded from this survival analysis (two from the acamprosate group and two from the placebo group), as they had participated in the screening and in the selection, but had not come to the first consultation (they had not received any kind of medication). Using the Log-Rank method, we obtained p=.017.

In the last week of the study 17 patients from the acamprosate group (42,5%) and seven from the placebo group (20%) were abstinent since the first consultation (p=.048, Fisher's Exact Test).

Side-effects reported by both groups, assessed by the UKU side-effect rating scale were diarrhea (p>.999), pruritus and skin macules (p=.612), headache (p=.612) and polyuria (p=.665). Daytime somnolence was reported by one patient (3%) of the acamprosate group and not by patients of the placebo group (p>.999, Fisher's Exact Test).

There was no statistically significant difference between both groups, regarding side-effects.

Three reasons for dropout were identified: protocol violation (not taking the medications, taking other forbidden medications), refusal to begin the treatment, and follow-up dropout. No patient reported intolerance to the medication under study. There was no statistically significant difference between both groups regarding reasons for treatment dropout (p=.861, chi-square test).

Discussion

Studies which assess efficient therapeutic strategies for the treatment of alcohol dependence have been performed, dealing with the multiple causal factors of this condition.

Assessing patients during a six-month follow-up we observed that in this clinical trial acamprosate was superior to placebo in treating alcohol-dependent subjects regarding the period of continuous abstinence.

Sass et al[18] (1996) performed a 48-week study with 272 alcohol-dependent patients who received acamprosate or placebo. At the end of the treatment, 39% of patients treated with acamprosate were abstinent, in contrast to 17% of patients of the placebo group, what was statistically significant (p=.003). Similar double-blind studies showed that acamprosate's efficiency was superior in terms of statistical significance when compared to placebo.[19-22] However, other studies comparing the efficacy of acamprosate and placebo in the treatment of alcoholism did not show any statistically significant difference.[23-25]

Regarding the medication's safeness, Lhuintre et al[26] found some side-effects, as follows: nausea (four patients of the acamprosate group versus 1 of the placebo group), erectile dysfunction (2 patients of the acamprosate group versus 1 of the placebo group) and pruritus (only 1 patient of the acamprosate group). Whitworth et al[19] reported that among some of the side-effects reported by patients diarrhea was the most frequent one in patients of the acamprosate group, what was statistically significant (p=.021).

In the present study, we observed some side-effects, as follows: diarrhea (four patients in the acamprosate group and three in the placebo group), pruritus and skin macules (three patients of the acamprosate group and one of the placebo group), daytime somnolence (one patient of the acamprosate group), headache (three patients of the acamprosate group and one patient of the placebo group), polyuria (two patients of the acamprosate group and three of the placebo group). There was no statistically significant difference regarding side-effects between the groups.

Sass et al[18] reported that 51% of patients were excluded from their study (dropouts) along the 12-month follow-up, mainly due to the refusal to proceed in the study and due to follow-up dropout, without any statistically significant difference between acamprosate and placebo groups. Withworth et al[19] reported that 59% of patients selected for their study were excluded from it during the 12-month follow-up, mainly due to severe relapses, loss of follow-up and refusal of patients to proceed the treatment, without any statistically significant difference between groups. Pelc et al[25] reported that 37% of selected patients dropped out during the 3-month fol-

low-up, mainly due to follow-up dropout and severe relapses.

In our study 17 patients did not complete the 24 weeks of the research (23%), being 10 patients from the acamprosate group and seven from the placebo group (p=.783), mainly due to the follow-up dropout (seven patients from the acamprosate group and four from the placebo group), refusal to begin treatment (two patients in the acamprosate group and two in the placebo group) and protocol violation (one patient in the acamprosate group and one in the placebo group), without any statistically significant difference between both groups.

In many studies which assess the efficacy of acamprosate compared to placebo the follow-up time period using the medication was longer than three months.[19,20,22] However, other studies were performed using a 3-month treatment period.[25,26]

In our study the total treatment period was six months, in the first three months patients received medication and in the following three months patients remained in the treatment without medication.

A limitation of our study was the small number of patients when compared to similar studies. Nonetheless, it was possible to demonstrate the superiority of acamprosate when compared to placebo in the treatment of alcohol-dependent subjects.

Conclusions

a) Acamprosate showed to be more efficient than placebo to maintain the abstinence in alcohol-dependent patients;
b) The proportion of abstinent patients was superior in the acamprosate group than in the placebo group;
c) Acamprosate was a safe and well-tolerated medication.

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