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Initiating acamprosate within-detoxification versus post-detoxification in the treatment of alcohol dependence

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Abstract

OBJECTIVES—This trial compared the efficacy of acamprosate, started at the beginning of detoxification, to acamprosate started at the completion of detoxification, in the treatment of alcohol dependence.

METHODS—This biphasic clinical trial consisted of a randomized, double-blind, placebo-controlled Detoxification Phase (DP), followed by a 10-week open-label Rehabilitation Phase (RP). Forty alcohol dependent patients were randomly assigned to receive either 1998 mg of acamprosate daily, or matching placebo, during the DP (5–14 days). After completing detoxification, all patients received open label acamprosate (1998 mg daily) in the RP. Outcome measures during the DP included: treatment retention, alcohol withdrawal, alcohol consumption, and oxazepam used. Outcome measures during the RP included: treatment retention and alcohol consumption.

RESULTS—There were no significant outcome differences between acamprosate and placebo-treated patients during the DP. Patients given acamprosate, compared to placebo, during the DP drank more alcohol in the RP.

CONCLUSIONS—Starting acamprosate at the beginning of detoxification did not improve DP outcomes. Starting acamprosate after detoxification was completed was associated with better drinking outcomes during subsequent alcohol rehabilitation treatment.

Keywords

acamprosate; alcoholism; detoxification; clinical trial; placebo

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1. Introduction

The Food and Drug Administration (FDA) approved the following indication for acamprosate: “The maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation” (Forest Pharmaceuticals, 2008). However, one of the proposed mechanisms of action of acamprosate is reduction of glutamatergic activity in alcohol dependent individuals during early abstinence. Glutamatergic activity in the brain is thought to be increased as a result of chronic alcohol administration (Dahchour & De Witte, 2000; Kumari & Ticku, 2000; Trevisan et al., 1994). This increase in glutamatergic activity is thought to contribute to symptoms of alcohol withdrawal during early abstinence (Dahchour & De Witte, 2000; Tsai, Gastfriend & Coyle, 1995; Tsai et al., 1998). By reducing glutamatergic activity, acamprosate may reduce symptoms of alcohol withdrawal during the post-acute phase and may reduce negatively reinforced relapses to drinking (Harris et al., 2003; Harris et al., 2002; Littleton, 2007). Based on this proposed mechanism of action, it would seem that acamprosate might be beneficial earlier in treatment, during acute detoxification. There are data from preclinical studies demonstrating that acamprosate reduces alcohol withdrawal in animal models (Abdelkader, Dahchour & De Witte, 2003; Dahchour et al., 1998). In addition, one open, clinical study and one controlled study of acamprosate showed that acamprosate given during the alcohol detoxification period did not cause any unwanted effects, and might possibly be an advantage in successfully achieving abstinence in the rehabilitation (post-detoxification) period of treatment (Aubin, Leher, Beaupere, Jacquemin & Barrucand, 1994; Gual & Leher, 2001). However, neither of these clinical trials was designed to test the comparison of initiating acamprosate in the detoxification versus post-detoxification period.

Another important and practical reason for initiating acamprosate during detoxification is that it takes approximately five days for acamprosate to achieve steady state therapeutic blood levels (Mason et al., 2002). This means that there will be a lag between the end of detoxification and the achievement of therapeutic blood levels of acamprosate in the post-detoxification or rehabilitation period. It has been shown that there is a high rate of treatment dropout in alcohol dependent patients in the interval between detoxification and rehabilitation treatments (Baekeland, Lundwall, & Shanahan, 1973). Delays in achieving therapeutic blood levels of acamprosate caused by starting treatment after detoxification may exacerbate the problem of drop out and otherwise negatively affect treatment outcome.

The purpose of this study was to begin to explore the timing of acamprosate initiation. Our hypothesis was that by starting acamprosate immediately during detoxification, instead of waiting until detoxification was complete, we could reduce alcohol withdrawal symptoms, reduce the expected dropout rate between detoxification and rehabilitation, and improve outcomes in the Rehabilitation Phase. This small pilot trial was intended to screen for differences between acamprosate given at the start of detoxification vs. acamprosate given at the completion of detoxification that could support an application for a larger double-blind, placebo-controlled study of medium to high power to more definitively test the study's hypothesis.

2. Methods

2.1 Patients

Study participants were recruited through community referrals and public announcements in the local media. Patients were invited to participate in a 12-week clinical trial that included two phases: a Detoxification Phase, and a post-detoxification Rehabilitation Phase. In order to be eligible to enter into the Detoxification Phase of the trial, patients needed to be between the ages of 18 and 70 years of age and meet DSM-IV criteria for current alcohol dependence, confirmed by the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). In

addition, patients were required to meet the following drinking criteria measured by the Timeline Follow Back (TLFB) (Sobell & Sobell, 1992): a. report a minimum of 48 standard alcoholic drinks (average of 12 drinks/week) in a consecutive 30-day period over the 90-day period prior to starting pharmacotherapy, b. have 2 or more days of heavy drinking (defined as 5 or more drinks per day in men and 4 or more drinks per day in women) within 30 days of starting pharmacotherapy treatment. All patients included in the trial were required to either have had a drink within 48 hours prior to their intake appointment or have a CIWA – Ar (Sullivan, Sykora, Schneiderman, Naranjo & Sellers, 1989) score equal to or greater than 3 on the day of intake. Patients needing medical detoxification were determined to be appropriate for outpatient detoxification as described below. Patients were required to be able to speak, print and understand English.

Patients were not included if they had a current DSM-IV diagnosis of any psychoactive substance dependence other than alcohol or nicotine. Patients were excluded for evidence of current use of other psychoactive drugs as determined by a positive urine drug screen. Patients could not be taking psychotropic medications (e.g., antidepressants, anxiolytic, antipsychotic, naltrexone, disulfiram, modafinil, stimulants or anticonvulsants), or have evidence of current severe psychiatric symptoms. Medical screening included a complete medical history and physical examination conducted by a certified nurse practitioner. Baseline laboratory testing included a chemistry screen, complete blood count, urinalysis, urine pregnancy testing (for women), and a 12 lead EKG. Patients could not have severe medical or physical illnesses. Patients could not have significant hepatocellular injury as evidenced by elevated AST or ALT levels greater than 5 times the upper limit of normal. Patients were excluded if they showed signs of impaired renal function as indicated by a corrected creatinine clearance below 80 ml/min/70 kg as determined by the modified Cockcroft equation (Cockcroft & Gault, 1976). Female patients who were pregnant, nursing, or not using a reliable method of contraception were also excluded. The study was reviewed and approved by the Institutional Review Board of the University of Pennsylvania, and all patients provided written informed consent prior to study participation.

2.2 Procedures

This trial was divided into two phases. The Detoxification Phase consisted of the screening visit as well as any visits necessary to meet inclusion criteria into the Rehabilitation Phase, which involved open-label acamprosate treatment. The Rehabilitation Phase consisted of weekly visits for 10 weeks.

Detoxification Phase—At the start of the Detoxification Phase, patients were randomly assigned to 1998 mg/day of acamprosate or matching placebo tablets for at least 5 consecutive days and no more than 14 consecutive days. During this time, patients were also allowed to receive medication (oxazepam) specifically for outpatient detoxification, if their withdrawal symptoms were deemed to require a medical detoxification.

Outpatient detoxification from alcohol was conducted by a highly trained and experienced team of certified nurse practitioners supervised by a board-certified addiction psychiatrist. A baseline medical history and physical examination was conducted at the first detoxification visit. Baseline laboratory tests such as blood chemistries, CBC, urinalysis and EKG were obtained at that time. Oxazepam was prescribed for the treatment of alcohol detoxification symptoms as needed based on the clinical judgment of the nurse practitioners, guided by scores on the Clinical Institutes Withdrawal Scale for Alcohol (CIWA-Ar). This instrument was administered at each detoxification visit. Oxazepam was dispensed at each detoxification visit and all unused medication was collected at the next visit. On Fridays, nurse practitioners prescribed enough medication to carry patients through until their next appointments, generally

the following Monday. Patients were contacted by phone on Saturday and Sunday to adjust weekend doses of oxazepam, as needed. In addition to oxazepam, patients received thiamine supplementation and a multivitamin. The only absolute contraindication to outpatient detoxification for this trial was a prior history of delirium tremens. Other relative contraindications include unstable medical problems, unstable living environment, and very severe alcohol detoxification severity (impending delirium tremens).

Oxazepam dosage was individualized, guided by CIWA-Ar scores. It was not discontinued until the patient achieved 3 consecutive days of abstinence from alcohol within a maximum of 14 days and had a CIWA-Ar score of 1 or lower.

Patients were not eligible to enter the Post-Detoxification Rehabilitation Treatment Phase open-label acamprosate plus a minimal counseling program called Medical Management (Pettinati et al., 2004; Pettinati et al., 2005) unless they had: 1) received at least 5 days of acamprosate or placebo, and 2) successfully completed outpatient detoxification within a 14-day period. Successful completion of detoxification was defined as having a score of 1 or lower on the CIWA -Ar, 2) at least 3 consecutive days of abstinence from alcohol, and 3) if applicable, have received no more than 45 mg of oxazepam within the 24-hour period prior to entering the Rehabilitation Phase.

Rehabilitation Phase—The Rehabilitation Phase consisted of 1998 mg/day of open-label acamprosate for 10 weeks with weekly, manualized, Medical Management visits (Pettinati et al., 2004; Pettinati et al., 2005). Medical Management is a psychosocial treatment intervention developed as part of NIAAA's COMBINE Trial that provides advice and support from medical staff concomitantly with dispensing medications and checking safety and compliance. The main goal of the intervention is to increase the likelihood that subjects will reduce their alcohol consumption and have favorable treatment outcomes. The initial Medical Management session is an hour; follow-up sessions last no more than 15–30 minutes. Acamprosate was dispensed weekly in blister packs. Patients were started on a dose of 666 mg three times daily at their first Rehabilitation Phase appointment. Medication was continued until the end of week 10 and then stopped.

2.3 Outcome Measures

The primary outcome measure for the Detoxification Phase was the percent of patients who successfully completed detoxification (as defined above). Secondary outcome measures for the Detoxification Phase included: (1) the total amount oxazepam prescribed, (2) the change in alcohol withdrawal symptom severity measured by the CIWA-Ar, (3) the total number of days duration of detoxification, and (4) the amount of alcohol drinking during outpatient detoxification.

The primary outcome measure in the Rehabilitation Phase was self-reported alcohol consumption as measured by the Time Line Follow-Back (TLFB) method (Sobell & Sobell, 1992). The TLFB method includes a semi-structured interview that uses a calendar format to record the quantity and frequency of drinking per day during a stated period of time. During the Rehabilitation Phase, drinking was assessed weekly. Quantity of alcohol was recorded in standard drinks (e.g., a 12-oz beer, a 5-oz glass of wine, or a 1.5-oz shot of 80 proof hard liquor = one standard drink). The alcohol consumption outcomes of interest were (1) percent days of any drinking (primary outcome measure), and other secondary outcome measures such as (2) percent days of heavy drinking (4 or more standard drinks per day for women, 5 or more standard drinks per day for men), and (3) drinks per drinking day.

Other secondary outcome measures included The Addiction Severity Index (ASI) (McLellan et al., 1992), which was administered at baseline and at the end of the trial. The Hamilton

Depression Rating Scale (HAM D) (Hamilton, 1967) and The Hamilton Anxiety Scale (HAM A) (Hamilton, 1959) were also administered at baseline and weekly through the Rehabilitation Phase. Alcohol craving was measured weekly using the Penn Alcohol Craving Scale (PACS) (Flannery, Volpicelli & Pettinati, 1999). Alcohol dependence severity was measured at baseline using the Alcohol Dependence Scale (ADS) (Skinner and Horn, 1982). Medication adherence was measured using a method of blister cards and pill counts (H. M. Pettinati, Volpicelli, Pierce & O'Brien, 2000). Treatment retention was measured by attendance at evaluation visits. Adverse events were monitored weekly by the nurse practitioner. Patients were asked at each evaluation visit if they had experienced any problems since the previous evaluation visit. Female patients received urinary pregnancy testing prior to starting medications, and at monthly intervals throughout the study.

2.4 Statistical Analysis

Baseline measures between the two groups (those who received Acamprosate during detoxification and those who received placebo) were compared using t tests for continuous variables and chi square tests for dichotomous variables. Nonparametric tests were used when the data were skewed. Drinking results were compared using Generalized Estimating Equations (GEE) models (Diggle & Kenward, 1994). These measures were analyzed both as binary (absence/presence) and continuous (quantity/frequency) repeated measures. GEE models were also used to compare the groups on other outcome measures, including Hamilton Depression and Anxiety Scales, Penn Alcohol Craving Scale, ASI results, and CIWA scales. The models generally included the pre-treatment version of the response as a covariate, together with treatment group, and time effects.

This study was exploratory and thus statistical power was only adequate to detect large effect sizes. The goal of this trial was to screen for differences between acamprosate given at the start of detoxification vs. acamprosate given at the completion of detoxification that could support an application for a larger double-blind, placebo-controlled study of medium to high power to more definitively test the study's hypothesis.

3. Results

3.1 Baseline Characteristics

Sixty-six patients signed consent and entered screening. Twenty-six patients did not meet inclusion/exclusion criteria and were excluded. Eight were excluded for medical reasons: three for poor renal function, two for poorly controlled hypertension, one for anemia, one for leukopenia, and one for an abnormal heart rhythm. Twelve were excluded due to drug abuse detected on a urine drug screen: ten patients had cocaine positive urines, and two patients had marijuana positive urines. Five patients were excluded due to other psychiatric diagnoses: two patients were cocaine dependent, two patients were marijuana dependent, and one patient had schizophrenia. One patient was excluded due to a low baseline CIWA score and no recent drinking. A total of 40 patients were entered into the Detoxification Phase of the trial.

For the overall sample, the mean age of the patients was about 48 years. Most were men (82%), and slightly more than half were Caucasian (58%). The mean number of years of education was 14.2 and 84 % of patients were employed at least part-time. Overall, patients drank a mean of 80 percent of days during the 90 days preceding detoxification, and drank heavily on an average of 71 percent of these days. Patients drank an average of 12.4 standard drinks per drinking day during this period. The average baseline score on the Alcohol Dependence Scale was 18.2. On the day of intake CIWA-Ar scores averaged 4.05. There were no significant differences in demographics, pre-treatment drinking data, baseline Alcohol Dependence Scale scores or baseline alcohol withdrawal symptom severity measured by the CIWA, between

patients treated with acamprosate and those treated with placebo during detoxification or during the rehabilitation phase (Table 1).

3.2 Detoxification Phase Outcomes

Thirty-four patients (85%) successfully completed detoxification. Detoxification Phase outcomes are summarized in Table 2. There were no significant differences between the acamprosate and placebo treated groups in the number of patients who successfully completed detoxification. There was no difference in time taken to achieve detoxification between the acamprosate and placebo treated groups. The mean total number of 15-mg. oxazepam tablets taken during detoxification did not differ between the acamprosate and placebo treated patients. CIWA scores declined in both the acamprosate and placebo treated patients but there was no significant difference noted between groups as determined by GEE analysis. Drinking during detoxification did not differ significantly between the acamprosate and placebo treated patients, measured by percent days of any drinking, percent days of heavy drinking or in drinks per drinking day.

3.3 Rehabilitation Phase Outcomes

Eighteen patients treated with acamprosate and 16 patients treated with placebo successfully completed detoxification and entered into the 10-week Rehabilitation Phase of the trial. Baseline demographics and drug use data of the 34 patients included in the Rehabilitation phase of the trial did not differ significantly between patients treated with acamprosate or placebo during detoxification (Table 1).

During this phase of treatment, all the patients received open-label acamprosate 666 mg three times daily. Five patients who had received acamprosate during detoxification did not complete the Rehabilitation Phase of treatment compared to four patients who had received placebo during detoxification, and there was no significant difference in completion rates.

Drinking outcomes during the Rehabilitation Phase of the trial favored patients treated with placebo during detoxification (Table 3). Patients treated with placebo reported a lower percent days drinking compared to patients treated with acamprosate (19% vs. 34%) but this difference was not statistically significant. Patients treated with placebo during detoxification reported a significantly lower percent days of heavy drinking, and reported significantly fewer drinks per drinking day during the Rehabilitation Phase of the trial compared to those patients treated with acamprosate during detoxification.

Other outcome measures obtained during the Rehabilitation Phase of treatment showed no significant differences between acamprosate and placebo detoxified patients (Table 4.). Alcohol withdrawal symptoms recorded weekly during the Rehabilitation Phase were not significantly different between the two groups. There were no significant differences between groups in alcohol craving measured by the Penn Alcohol Craving Scale. There were declines in Hamilton Anxiety and Depression Inventory scores but no significant differences noted between the two groups. Finally changes in ASI composite alcohol scores showed no significant differences between the two groups.

3.4 Medication adherence

Medication adherence was measured by pill count. The percentage of pills taken was calculated by subtracting the number of pills returned each week from the number of pills dispensed. Medication adherence during the Detoxification Phase was good for both groups and did not differ significantly between groups (91% acamprosate vs. 87% placebo, $t = -.56$, $df = 34$, ns). However, adherence to open label acamprosate during the 10-week Rehabilitation Phase differed significantly between those patients who received acamprosate and those patients who

received placebo during detoxification. Acamprosate detoxified patients took significantly fewer of the open label acamprosate prescribed to them, compared to patients who received placebo during detoxification (61% acamprosate vs. 84% placebo, Mann-Whitney U, $z = -2.28$, $p = .02$).

When differences in medication adherence during open label acamprosate were taken into account the direction of effect did not change but the significance level did for outcome measures including percent days drinking (wald $\chi^2 = 0.13$, $p = .72$), percent days heavy drinking (wald $\chi^2 = 1.45$, $p = .23$) and drinks per drinking day (wald $\chi^2 = 2.14$, $p = .07$). In all three cases, patients who received acamprosate during detoxification drank more during the open label phase, but the differences between patients who received acamprosate during detoxification versus those who received placebo during detoxification were no longer statistically significant.

3.5 Safety analyses

Adverse events were assessed at each visit. Acamprosate was generally well tolerated. There were five serious adverse events; none were medication related. Three patients were admitted to inpatient drug and alcohol facilities for detoxification due uncontrolled drinking (two assigned to acamprosate and one to placebo). One patient was admitted to a hospital for a gastrointestinal hemorrhage (acamprosate). One patient was admitted to a hospital for uncontrolled hypertension (acamprosate). All five patients recovered completely. Adverse events were mainly mild and evenly distributed between the acamprosate and placebo groups. The most commonly reported adverse events included aches and pains ($n=11$), upper respiratory tract infection ($n=7$), diarrhea ($n=7$), headache ($n=7$), and skin rash ($n=7$). There were no significant differences between the occurrence of any adverse event and assignment to acamprosate or placebo during detoxification.

4. Discussion

Acamprosate did not appear to provide any benefit over placebo in reducing dropout or otherwise improving detoxification outcomes in alcohol dependent patients participating in outpatient detoxification. In this trial, dropout during detoxification was relatively rare (15%), and dropouts were evenly distributed between acamprosate and placebo treated patients (16% for acamprosate and 14% for placebo). Acamprosate treatment **did not reduce**: the duration of detoxification, the amount of benzodiazepines taken during detoxification, alcohol withdrawal symptom severity experienced during detoxification, measured by the CIWA-Ar, or the amount of drinking during detoxification.

Starting acamprosate during detoxification, instead of starting it after patients had successfully completed detoxification and were abstinent for at least 3 days, did not provide any benefit in a subsequent 10-week outpatient alcohol treatment trial. In fact, patients who started acamprosate during detoxification appeared to have worse drinking outcomes compared to those treated with placebo during detoxification. Patients given acamprosate during detoxification reported a significantly higher percent days of heavy drinking and drank significantly more drinks per drinking day during a 10-week outpatient trial that included open-label acamprosate and weekly medication management sessions. Patients who received acamprosate during detoxification took fewer of their prescribed open-label acamprosate pills during the Rehabilitation Phase of treatment compared to patients who had received placebo during detoxification.

The fact that acamprosate did not improve detoxification outcomes, and that patients treated with acamprosate during detoxification appeared to drink more alcohol in the subsequent 10-week outpatient trial were both unexpected results. That is, we had predicted, based on

acamprosate's proposed mechanism of action, that acamprosate could be beneficial during detoxification. Also, in several animal models acamprosate reduced alcohol withdrawal symptom severity. In human laboratory trials, acamprosate ameliorated sleep disturbances associated with alcohol withdrawal and reduced brain hyperexcitability associated with alcohol withdrawal (Boeijinga et al., 2004; Staner et al., 2006). At least one previous outpatient trial has shown that acamprosate was more effective than placebo when started from the day of intake (Gual & Leher, 2001). However, no previous study has compared the efficacy of acamprosate initiated at the start of detoxification to the efficacy of acamprosate started after patients have successfully completed detoxification and achieved at least five days of abstinence from alcohol.

Evidence from most clinical trials suggests that acamprosate may be more efficacious in patients who have attained abstinence from alcohol prior to initiating treatment. In the three European trials used to obtain US FDA approval of acamprosate, 95% of the subjects were abstinent from alcohol at the start of acamprosate treatment. In contrast, in two large negative trials, one conducted in the United Kingdom and one conducted in the United States, 30% and 51% of the subjects, respectively, had resumed drinking prior to randomization (Kranzler & Gage, 2008). A large meta-analysis of acamprosate clinical trials, including 4457 subjects, showed that detoxification prior to starting acamprosate was associated with better outcomes (Lipha Pharmaceuticals, 2002). Why acamprosate appears to be more efficacious after a longer duration of abstinence has not been determined. However, in a rodent model, the activity of acamprosate at the NMDA receptor in vitro has been shown to be dependent on prior exposure of the brain to alcohol (al Qatari, Bouchenafa, & Littleton, 1998). It may be that the activity of acamprosate at NMDA receptors is different in the presence of very recent alcohol use compared to after patients have been detoxified and free from alcohol for several days.

Why exposure to acamprosate during detoxification phase affected subsequent medication adherence in the rehabilitation phase is not known. It is possible that starting acamprosate during detoxification alters the adverse effect profile of acamprosate leading to poor adherence. If this occurred during the trial, it was not detected by a comparison of the rates of adverse events, which did not differ between the two groups. It is also possible that starting acamprosate during detoxification reduced its beneficial effects and patients simply stopped taking acamprosate because they could detect no benefit from the medication.

This trial has several weaknesses. The number of patients was relatively small and thus the results should be considered preliminary. In addition, patients admitted into this trial had to be suitable for outpatient detoxification and may not have been reflective of the population of alcohol dependent patients in general. The reported alcohol withdrawal symptom severity as measured by the CIWA was relatively low and, based on our results, it is impossible to say if acamprosate would have been more useful in the detoxification of alcohol dependent patients who presented with more severe alcohol withdrawal symptoms. However, a meta-analysis of acamprosate clinical trials involving 1485 patients did not show that withdrawal symptom severity or alcohol dependence severity at baseline were predictors of acamprosate efficacy (Verheul, Leher, Geerlings, Koeter & van den Brink, 2005). In addition, acamprosate detoxified patients in this trial consumed alcohol on average, 80% of the days in the month prior to entry. They consumed an average of 15 standard drinks per drinking day during this time (slightly more than the average of 12.4 drinks per day over the entire 90 day pretrial period). This rate of drinking is comparable to the rate of drinking noted in the three pivotal trials of acamprosate. In those trials, 73% of patients drank more than 10 standard drinks per day. Thus, patients in the current trial were drinking at rates that were comparable to patients included in previous trials in which acamprosate was found to be efficacious.

Although only powered to detect large effects, it is unlikely that this trial failed to detect a significant advantage to starting acamprosate at the beginning of detoxification because of its relatively small sample size. The differences between acamprosate and placebo treated patients noted in the main Detoxification Phase outcome measures were extremely small and, in fact, most (5/7) numerically favored placebo over acamprosate. In the Rehabilitation Phase, drinking outcomes, including percent days heavy drinking and drinks per drinking day were statistically significantly greater among patients who received acamprosate during detoxification.

Conclusions

Despite its weaknesses, the results of this trial suggest that initiating acamprosate at the start of an outpatient detoxification does not improve treatment retention or otherwise improve detoxification treatment outcomes. In addition, initiating acamprosate during outpatient detoxification did not improve outcomes in subsequent rehabilitation treatment and appeared to worsen drinking outcomes, compared to patients who started acamprosate after detoxification was completed, and who had attained, at least, 3 days of abstinence. The data do not support the initiation of treatment with acamprosate during outpatient detoxification.

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Table 1
Baseline demographics and drinking data expressed as means (standard deviation) or percents.

	Acamprosate during detoxification n=21	Placebo during detoxification n=19	Acamprosate during rehabilitation n=18	Placebo during rehabilitation n=16
Age	47.9 (11.0)	47.2 (10.3)	49.3 (11.3)	48.5 (9.6)
% Male	80	84	83	81
%Caucasian	57	58	61	56
%Married	30	28	35	31
Education	14.2 (2.6)	14.4 (2.2)	13.9 (2.4)	14.5 (2.2)
% Employed	90	76	79	79
% Days Drinking	80.2 (19.9)	78.3 (20.8)	79.0 (20.6)	79.0 (19.5)
% Days of Heavy Drinking	72.8 (26.7)	69.1 (29.2)	70.3 (27.6)	68.4 (30.0)
Drinks/Drinking Day	14.7 (7.6)	11.2 (4.6)	13.5 (7.4)	10.3 (3.8)
ASI Alcohol Composite Score	.720 (.108)	.644 (.145)	.704 (.100)	.634 (.140)
Hamilton 17 Item Depression Score	10.9 (6.6)	9.7 (7.0)	9.6 (6.0)	9.3 (6.5)
Hamilton Anxiety Score	8.9 (7.3)	8.8 (8.2)	7.2 (5.9)	7.8 (6.8)
Alcohol Dependence Score	19.9 (10.6)	16.4 (7.2)	18.0 (10.3)	15.6 (7.3)
CIWA AR	4.0 (3.3)	4.2 (5.4)	3.6 (2.7)	3.6 (3.7)

Table 2

Detoxification Phase Outcomes expressed as percents or means (standard deviation).

	Acamprosate during detoxification n=21	Placebo during detoxification n=19	Test Stat	p
% who completed detoxification	86%	84%	.02 *	.89
Days of detoxification	7.3 (1.6)	6.8 (1.5)	.88 **	.38
# of 15 mg. oxazepam tabs. taken	14.6 (11.2)	9.9 (12.3)	-1.1 **	.28
Change in CIWA scores	-2.6 (2.9)	-2.8 (3.5)	<.01 ***	.97
% days drinking	9.1 (16.8)	12.5 (18.0)	.58 **	.56
% days heavy drinking	6.5 (16.6)	6.0 (14.1)	-.90 **	.93
Drinks per drinking day	2.0 (3.6)	1.6 (2.3)	-.34	.74

* Chi square

** t test

*** Wald χ^2

Table 3

Rehabilitation Phase Drinking Outcomes expressed as means (standard deviation).

	Acamprosate during detoxification n=18	Placebo during detoxification n=16	Main Effect of Medication	
			Wald χ^2	p
Days Drinking (%)	33.7 (28.9)	19.4 (26.9)	2.36	.12
Days Heavy Drinking (%)	29.6 (29.8)	11.0 (18.9)	5.34	<.01
Drinks per drinking day	8.1 (6.9)	4.7 (3.9)	4.48	.03

Table 4
Other Outcomes. Baseline and end of study values expressed as means (standard deviation).

	Acamprosate during detoxification n=21		Placebo during detoxification n=19		Main Effect of Medication	
	Baseline	End of Study	Baseline	End of study	Wald χ^2	P
PACS	20.4 (6.4)	11.1 (8.7)	18.9 (8.8)	10.7 (10.6)	.01	.94
HAM D	10.9 (6.6)	5.8 (5.6)	9.7 (7.0)	6.6 (7.7)	<.01	.99
HAM A	8.9 (7.3)	4.5 (5.0)	8.8 (8.2)	4.9 (5.6)	.09	.77
ASI Alcohol Composite	.644 (.145)	.283 (.300)	.719 (.107)	.194 (.291)	1.85	.17