Alcohol & Alcoholism Vol. 36, No. 5, pp. 413–418, 2001

ACAMPROSATE DURING AND AFTER ACUTE ALCOHOL WITHDRAWAL: A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY IN SPAIN

A. GUAL* and Ph. LEHERT[1]

Unitat d'Alcohologia de la Generalitat, IMD, Hospital Clínic, Villarroel 136, 08036 Barcelona, Spain and [1]Department of Statistics, University of Mons, FUCAM, 151, Chaussée de Binche, B-7000 Mons, Belgium

(*Received* 3 *February* 2000; *in revised form* 2 *March* 2001; *accepted* 31 *March* 2001)

Abstract — To test acamprosate's role as an aid in preventing relapse after detoxification, 296 alcohol-dependent patients entered a prospective, multicentre, randomized, double-blind, parallel comparison of acamprosate treatment consisting of two 333 mg tablets given three times daily for 180 days with matching placebo treatment. Unlike previous studies, acamprosate was prescribed from the start of alcohol withdrawal, rather than after the detoxification process. During the treatment period, 110 patients dropped out. The two treatment groups were balanced with regard to baseline values and reasons for discontinuation. There was no difference between the groups in the severity of withdrawal symptoms as measured by the CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol scale). Acamprosate given during withdrawal did not cause unwanted effects. The cumulative abstinence duration (CAD, main end-point) was 19 days longer in the acamprosate treatment group than the placebo treatment group (analysis of variance on ranks, $P = 0.0006$) and the stable recovery duration, defined as the number of abstinent days between the last relapse into any drinking and the end of the trial, was 16 days longer in the acamprosate treatment group ($P = 0.021$). Continuous abstinence, estimated by survival analysis on time to first relapse, was achieved by 35% of acamprosate-treated patients and 26% of placebo-treated patients (log rank $P = 0.068$). The geometric mean of the ratio final/baseline values for serum carbohydrate-deficient transferrin was 0.802 (placebo) and 0.733 (acamprosate) ($P = 0.059$). The geometric mean of the ratio final/baseline values for serum γ-glutamyltransferase was 0.496 (placebo) and 0.415 (acamprosate) ($P = 0.024$) which corroborated the greater abstinence reported by the acamprosate group.

INTRODUCTION

Chronic alcoholism is a major public health concern in Spain, as in all industrialized countries. The ideal therapeutic approach should properly address its complex multi-dimensional biological, psychological and social aspects. Individual or group psychotherapy and social support measures directed to the psychological and social dimensions of alcoholism have now proven their usefulness. However, the lack of a specific pharmaceutical agent able to treat the biological basis of alcohol dependence has compromised the long-term success rates of these psychosocial interventions. Over the last two decades, significant advances in alcoholism research have been unveiling the basic molecular mechanisms involved in alcohol dependence. Research findings suggest that an alcohol-induced neurotransmission imbalance is one of the underlying biological mechanisms for alcohol dependence, and that pharmacotherapy could play an important role in treatment (Chick and Erickson, 1996).

Acamprosate (calcium acetylhomotaurinate) has been postulated to act by restoring the alcohol-induced neurotransmission imbalance of inhibition–excitation inputs believed to underlie alcohol dependence (Zeise *et al.*, 1993; Littleton, 1995). The molecular structure of acamprosate explains its specificity towards the basic molecular mechanisms involved in the physiopathology of alcohol dependence. Naassila *et al.* (1998) found a competitive interaction between spermidine and acamprosate, suggesting a specific binding site for acamprosate on *N*-methyl-D-aspartate receptors. Clinical research established acamprosate's safety and its specific ability to help maintain abstinence in different alcohol-dependent populations in Europe (Paille *et al.*, 1995; Sass *et al.*, 1996; Whitworth *et al.*, 1996; Poldrugo, 1997). Acamprosate seems to have a direct effect on alcohol consumption, without affecting any other function or disorder of the central nervous system (W. M. Hermann, unpublished report).

In the other European studies, acamprosate therapy was introduced after the administration of acute alcohol weaning therapy with the patient remaining abstinent for at least 5 days before the introduction of acamprosate. In the present study, acamprosate was introduced from the first day of detoxification, thus allowing even patients with a tendency to 'immediate drop-out', as described by Baekeland *et al.* (1973), to be started on the drug. Furthermore, since steady-state levels of acamprosate are only achieved by the fifth treatment day (Saivin *et al.*, 1998), it was considered that this regime would allow optimal effect earlier after acute withdrawal than when the study medication commences a week or two after acute withdrawal. An open clinical study using acamprosate prescribed together with benzodiazepines, barbiturates and tranquillizers during 2 weeks of medicated withdrawal showed no unwanted interactions (Aubin *et al.*, 1994).

In addition to efficacy assessment during the post-detoxification phase (main end-point), the present study provided the opportunity to assess the safety of acamprosate during withdrawal in a double-blind trial. Most of the above-mentioned studies used acamprosate at a dose of 1998 mg (six tablets) per day for patients >60 kg and at a dose of 1332 mg (four tablets) per day for patients <60 kg. However, titrating the dose does not seem to be supported by sufficient objective evidence (Saivin *et al.*, 1998) and therefore in this study all patients received six tablets per day, to investigate the tolerance profile of the drug under such prescription conditions.

*Author to whom correspondence should be addressed.

SUBJECTS AND METHODS

The study was a prospective, randomized, double-blind, parallel comparison of acamprosate treatment consisting of two 333 mg tablets given three times daily for 180 days with matching placebo treatment, also two tablets administered three times daily. The primary objective was to evaluate the efficacy of acamprosate, prescribed from the start of alcohol withdrawal, in supporting abstinence in alcohol-dependent volunteer patients.

Subjects and their alcohol history and craving

A total of 296 patients aged 18–65 years with a diagnosis of alcohol dependence for at least 1 year who agreed to embark on a programme of abstinence and who had consumed alcohol in the previous 7 days were included from 11 centres in Spain. The diagnosis of alcohol dependence had to conform to the DSM-III-R criteria of the American Psychiatric Association (1987). All patients gave written informed consent and the ethics committees of all participating hospital centres, according to Spanish regulations, approved the study protocol. Among the exclusion criteria were patients with psychiatric illness that would require specific drug treatment during the clinical trial and patients who had abused any other drug (excluding tobacco) during the preceding 6 months. Systematic urine screening for drugs of abuse was not part of the intake procedure.

Procedures

Following randomization (day 0), patients attended the clinic for assessment on treatment days 8, 30, 60, 90, 135 and 180. Alcohol withdrawal therapy was to be administered on either an in-patient or out-patient basis. Withdrawal symptoms were assessed by the Addiction Research Foundation's Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar; Sullivan *et al*., 1987). This is a 10-item rating scale of acute withdrawal symptoms rated by the attending physician. Nine symptoms are scored from 0 to 7 and one symptom from 0 to 4, where 0 designates absence of the symptom and the maximum score designates its most severe degree, adding up to a maximum total score of 67. In this study, the scale was used on the first and seventh days of withdrawal. Tetrabamate or chlomethiazole were permitted as acute withdrawal medication during the first 14 days, but not beyond. For the remainder of the study, if an antidepressant was indicated, amitriptyline or imipramine were permitted. For anxiolytic medication, chlordiazepoxide or dipotassium clorazepate was permitted for a period not exceeding 15 days, and triazolam or temazepam as hypnotic, if sleep disturbances warranted it.

If the patient could not be contacted for follow-up visits, a family member previously identified as responsible for supervising the patient was contacted in order to establish the reason.

The baseline variables included demographic, physical, emotional, mood, family antecedent, scoring for the MAST (Selzer, 1971), a complete history of the pathology, alcoholism specific and individual DSM-III-R item-related variables. Symptoms of acute withdrawal were measured on the first and seventh days of acute withdrawal by using the CIWA-Ar scale as discussed above. At each visit, alcohol intake during the previous period was documented by several variables, including mean frequency and quantity. Craving was measured by a 4-point self-rating scale ranging from 1 (indifference to alcohol) to 4 (an uncontrolled desire for alcohol), and general 'improvement' was rated by the interviewer on a 3-point scale according to whether the general condition had improved since the start of the study, remained unchanged or worsened.

Statistical assessment

Populations. The main efficacy analysis was carried out on an intention-to-treat (ITT) basis. Thus all patients who were randomized took at least one dose of study medication and provided any key data after baseline were included in the analysis of outcome (the ITT sample). Secondary analyses considered two other populations. All the randomized patients (whole sample, W sample) irrespective of existence of key data after baseline comprised the W sample. Finally, we considered the per protocol or efficacy evaluable sample as patients with a normal trial termination, or experiencing a premature end for reasons unrelated to alcoholism (e.g. disc hernia, epilepsy unrelated to alcoholism, long-standing renal tumour and an episode of mania).

Primary and secondary end-points. At each visit V_i after baseline, and for the corresponding period (V_{i-1}, V_i), the patient was classified as completely abstinent, relapser, or missing. Complete abstinence was attributed when the patients self-declared abstinence during the whole period, and this abstinence was confirmed by a γ-glutamyltransferase (γ-GT) concentration less than the baseline value up to 60 days after baseline or a γ-GT <1.3 times the upper limit of normal (Potgieter and Lehert, 1996) from 60 to 180 days. The cumulative abstinence duration (CAD) is simply the duration of the abstinent periods (by default, periods of relapse or with missing observation are systematically together considered as relapse periods). CAD is considered as the best compromise between accuracy of abstinence estimate and representativeness (Lehert, 1993) and constituted the main end-point of this analysis.

Other supportive (secondary) end-points were: (1) time to first relapse (TFR), defined as the first time since the beginning of the trial, where patients drank any alcohol; (2) stable recovery duration (SRD) defined as the number of abstinent days between the last relapse into any drinking and the end of the trial; (3) mean change in γ-GT; (4) mean change in carbohydrate-deficient transferrin (CDT).

Statistical analysis. The two treatments were compared on CAD by adjusting by initial severity. As the initial severity of the patient's condition seemed to be best measured by the DSM-III-R classification of mild, moderate and severe, instead of an analysis of covariance (ANCOVA) adjusting for initial severity, a two-way analysis of variance (ANOVA) was used with two fixed factors: 'treatment' and 'initial severity', and their interaction. Furthermore, as CAD distribution might depart from a normal distribution, non-parametric ANOVA or ANOVA on ranks was carried out providing a generalization to Kruskal–Wallis test for general ANCOVA and ANOVA models. Time to first relapse was analysed by a survival technique where all patients lost to follow-up were considered as relapsed at the time of the first relapse or the first missing value, and the significance of the difference between the two treatments was assessed by a log rank test, with adjustment for centres.

The analysis of data on γ-GT and CDT was carried out in comparing the final/baseline ratio by an ANOVA on logarithmic transformed values, adjusting for gender (given the expected differences between male and female patients). Mean changes were expressed as geometric means. The final value was estimated by the last observed value carried forward.

RESULTS

Recruitment and retention

Of the initial 296 patients, one patient (randomized to acamprosate) never received study medication, leaving 295 who entered into the acute detoxification treatment taking study medication. All safety data in the study were reported on this population. Seven patients (six on acamprosate and one on placebo) left the acute detoxification period without any data on key variables after day 0. The ITT sample thus consisted of 288 patients [141 placebo (p) + 147 acamprosate (a), Fig. 1]. From these, 102 patients (57p + 45a) prematurely discontinued the trial (Table 1); the predominant reason was loss to follow-up (21a + 27p). For both treatment groups, the number of patients withdrawn for each individual reason was similar. Finally, 263 patients (128a +135p) were in the efficacy evaluable sample, and 186 (90p + 86a) completed the study.

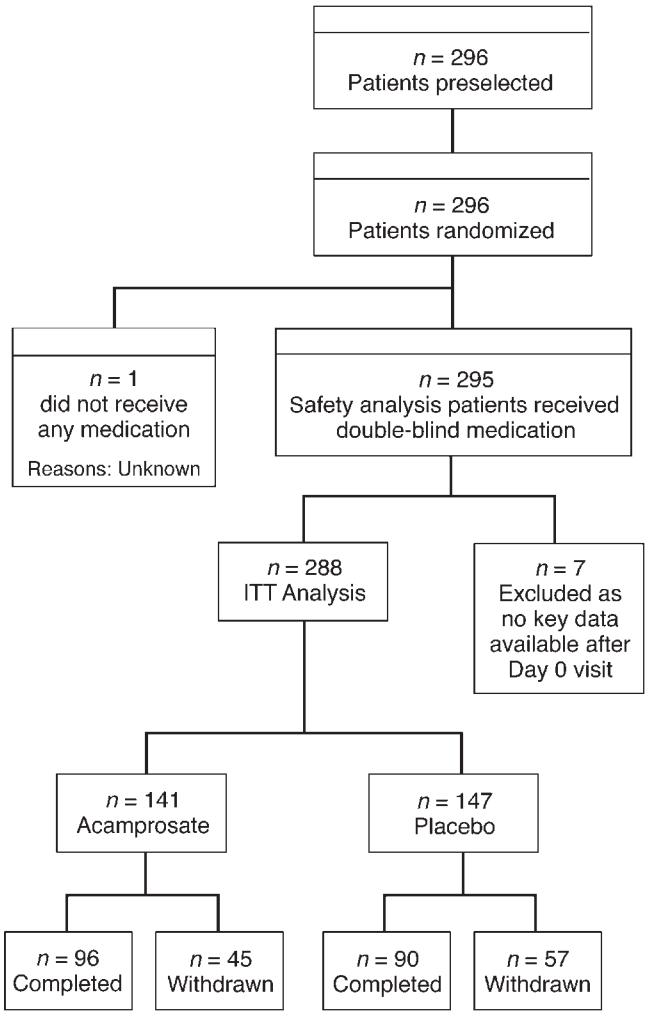

Fig. 1. Recruitment, randomization and retention.

Table 1. Main reason for study discontinuation (randomized patients)

Reason for discontinuation	Acamprosate (n = 148)	Placebo (n = 148)
No medication	1	0
No data after baseline	6	1
Intent-to-treat sample	141	147
Adverse event	2	1
Concurrent illness	1	3
Lost to follow-up	21	27
Severe relapse	4	7
Protocol violation	9	7
Refusal to continue	5	10
Lack of compliance	3	2
Ending normal time	96	90

The treatment groups matched well with regard to all baseline values. There were no statistically significant differences between the two groups (Table 2). Twenty-six per cent of patients weighed <60 kg, with an equal distribution between treatment groups.

Acute withdrawal period

All the patients were treated as out-patients. Fifty in each group did not receive specific detoxification medicine, and the others received either tetrabamate (n = 115) or chlomethiazole

Table 2. Clinical and demographic data (intention-to-treat population)

Variable	Acamprosate n = 141	Placebo n = 147	Significance (P)
Age (years)[a]	41.40 ± 9.01	40.69 ± 9.47	0.77
Sex			
Male	113 (80)	116 (79)	0.79
Female	28 (20)	31 (21)	
Weight (kg)[a]	67.8 ± 12.66	69.18 ± 13.44	0.076
DSM-III-R total index[a]	7.73 ± 1.36	7.80 ± 1.31	0.76
Alcohol quantity (drinks per typical drinking day)*			
<5	6 (4)	5 (3)	0.76
5–10	45 (32)	41 (28)	
>10	90 (64)	101 (69)	
Frequency of alcohol consumption			
Twice a week	3 (2)	3 (2)	0.71
More than twice	22 (16)	18 (12)	
Daily	116 (82)	126 (86)	
Consumption type			
Episodic	22 (16)	16 (11)	0.24
Continuous	119 (84)	131 (89)	
Antabuse (disulfiram prescription)			
No	78 (74)	73 (70)	0.52
Yes	27 (26)	31 (30)	
Total MAST score[a]	28.270 ± 8.01	27.38 ± 8.95	0.38
Dependence duration (years)	12.64 ± 8.28	12.9 ± 7.59	0.78

*A drink was defined as any drink containing 10–12 g of pure alcohol.
Values in parentheses are percentages.
[a]Mean ± SEM.

Table 3. Abstinence end-points

Patient population, treatment, *P*-value	Continuous abstinence (% of patients who never drank during the study)	Cumulative abstinence duration (CAD) (days)	Stable recovery duration (SRD) (days)
Intention to treat (n = 288)			
Acamprosate	35	93 ± 75	64 ± 81
Placebo	26	74 ± 75	48 ± 75
P =	0.068	0.006	0.021
Efficacy evaluable population (n = 263)			
Acamprosate	35	95 ± 74	65 ± 81
Placebo	26	72 ± 75	48 ± 76
P =	0.055	0.002	0.024

CAD and SRD values are means ± SD.

(n = 57), equally reported among treatment groups. The mean duration of withdrawal treatment (including tetrabamate, chlomethiazole, other anxiolytic medication, and triazolam or temazepam as hypnotic, if necessary) was similar in each treatment group (means ± SD): 17.6 ± 10.7 days for acamprosate compared with 20.4 ± 11.5 days for placebo. The CIWA-Ar scores were recorded at the beginning of acute detoxification and after 1 week. The mean drop in score was 7.25, with no statistical difference between the two treatment groups (7.45 in the acamprosate group and 7.04 in the placebo group). Patients who received detoxification medicine had a slightly bigger drop (7.86) against patients who did not (6.41), without a significant difference.

Outcome criteria

ITT analysis. The CAD estimates were 93 ± 75 days (acamprosate) and 74 ± 75 days (placebo) with 19 days longer in the active tested treatment group (two-way ANOVA on ranks, treatment effect, P = 0.006). For stable recovery duration (SRD), the period after the last relapse was 16 days longer in the acamprosate treatment group (P = 0.021). The rate of complete abstainers was estimated by survival analysis of the time to first relapse over 6 months of treatment, and was 35% and 26% on acamprosate and placebo respectively (log rank P = 0.068). Whole sample: a supportive study was carried out, categorizing the patients without any key data after baseline as a total failure (CAD = 0). Results were essentially unchanged: 72.23 ± 74.92 days and 88.88 ± 75.72 days for the acamprosate and placebo treatment groups, respectively (two-way ANOVA on ranks, treatment effect, $P < 0.035$).

Efficacy evaluable population. As shown in Table 3, differences between the two treatment groups were enhanced, as expected, compared with the main ITT results.

Predictors

Several general linear models carried out on possible interaction between baseline variables and cumulative abstinence duration could not identify any clear predictors for study medication response. Some variables showed a tendency toward interactions, but in such an inconsistent or statistically non-significant way that these were probably related to alpha error, and did not suggest a reliable predictor profile.

Other outcome criteria

The secondary efficacy variables included craving and the patient and investigator scoring of general improvement. The mean craving score was not significantly different between the two treatment groups at any time point, but the number of patients who recorded 'no craving' ('indifference to alcohol') was higher and the duration with 'no craving' was longer in the acamprosate group (Table 4).

Of the secondary outcome criteria, the following showed a statistically significant advantage for patients treated with acamprosate: self-report of duration with little or no craving (P = 0.07), the cumulative duration of the periods of improvement as assessed by the investigator (P = 0.05) and the percentage of patients and the cumulative duration of the periods of improvement as assessed by the patient retrospectively (P = 0.044 and P = 0.01).

Objective markers

γ-GT and CDT were used as objective markers for alcohol consumption. The geometric mean (SEM) of the ratio final CDT/baseline CDT was 0.802 (0.042), and 0.733 (0.042) for the placebo and acamprosate groups respectively (ANOVA adjusted on gender, P = 0.059). The geometric mean (SEM) of the ratio final γ-GT/baseline γ-GT was 0.496 (0.04), and 0.415 (0.04) for the placebo and acamprosate groups respectively (ANOVA adjusted on gender, P = 0.024).

Table 4. Secondary variables of efficacy

Craving	% of patients who recorded no craving for alcohol (indifferent)	Total duration with no craving (days)
Acamprosate	26	89 ± 74
Placebo	16	80 ± 73
P =	0.52	0.07
Success scored by the investigator	**% of successful patients**	**Total duration successful treatment (days)**
Acamprosate	55	128 ± 67
Placebo	50	119 ± 71
P =	0.335	0.05
Success scored by the investigator	**% of successful patients**	**Total duration successful treatment (days)**
Acamprosate	62	136 ± 63
Placebo	51	123 ± 67
P =	0.044	0.01

A Pearson correlation matrix was performed including drinking variables and the two objective markers. This matrix showed low correlation between γ-GT and CDT. For example, at visit 6 the correlation coefficient (r) between these two markers was 0.165. However, it became apparent that the correlation improved if the γ-GT at visit 6 was compared to the CDT values of the present and preceding visit (visits 5 and 6) which gave $r = 0.185$ and the correlation further improved if compared with CDTs of three visits (visits 4, 5 and 6), giving an $r = 0.195$. However, the correlation decreased again when adding CDT values of more than 2 visits before the measuring visit. This type of temporal model therefore suggested a delay in rise in γ-GT in comparison to CDT, for up to three assessment periods, implying that CDT rose sooner and γ-GT later after a drinking episode. This finding was also reported by Mitchell *et al.* (1997).

Concomitant medication

The most frequently prescribed concomitant medication during the post-detoxification period was tranquillizers. Sixty-three per cent of acamprosate patients and 65% of placebo patients consumed tranquillizers at some stage during the study, but the distribution of concomitantly prescribed medication was similar in each treatment group. Disulfiram and medication with a disulfiram-like effect was not permitted.

Compliance

In the 62% who completed the study, the mean number of tablets taken per day was 5.49 and 5.87 in placebo and acamprosate groups respectively.

Safety evaluation

The overall incidence of adverse events was similar in both treatment groups. The number of patients who presented at least one new (not present at baseline) adverse event during the course of the study was 99 on acamprosate and 94 on placebo. Nevertheless, there was a trend for gastrointestinal adverse events to be reported more frequently in the acamprosate-treated patients ($n = 61$) compared with placebo-treated patients ($n = 46$). The individual adverse events which were reported more frequently in association with acamprosate were diarrohoea, dyspepsia, constipation and flatulence. Pruritis was reported by seven in the acamprosate group and five in the placebo group.

There was no indication of any interaction between the study medication and the acute detoxification medication used in the first 2 weeks of the study. Furthermore, the frequency and profile of adverse events was the same in patients <60 and >60 kg.

DISCUSSION

The choice of outcome criteria resulted in interesting differences in the results of this study. In addition to known outcome criteria for drinking behaviour, such as the time to first drink and the cumulative abstinence duration, which have been used in many acamprosate and other studies, this study also measured the stable recovery duration (SRD) — the duration of abstinence after the last relapse until the end of the study. The rationale for this is that time to first relapse does not give any information on the drinking pattern after the first relapse, and the simple cumulating of abstinent days, such as in CAD, could, for example, hide a difference between continuous short relapses going on until the end of the study and one long relapse early on in the study with a long stable abstinence for the rest of the period. In our opinion, the latter patient would probably finish a study with a better expectancy to remain abstinent after termination of the study treatment. It therefore seemed reasonable to test the hypothesis that the accumulation of abstinent days (as in CAD) could allow a projection on the duration of continuous abstinence after the last relapse, by measuring the period after last relapse. The measure of SRD is useful for such assessments and in future can be examined as a potential measure to predict prognosis after the treatment period. Our study could not measure this latter potential owing to the absence of a follow-up period after terminating the study medication.

Patients on acamprosate had a mean of 16 days (~9% of study duration) longer continuous abstinent periods after last relapse (SRD) than placebo patients (further research with this type of measure would be interesting) and a mean of 19 days (~11% of study duration) longer CAD. Although in principle the SRD measures something different from the CAD, in our study, which was limited to the period of active study medication, the apparent advantage for patients on acamprosate, as shown by the CAD, was simply confirmed by the SRD. The SRD during study treatment may, nevertheless, be a useful outcome measure, if examined more thoroughly in studies where it can be compared with abstinence duration during treatment-free follow-up periods, in order to assist in determining possible prognostic indicators.

The combination of the three primary outcome measures in this study allowed us to conclude that patients on acamprosate had their first relapse later than patients on placebo (but this difference was not statistically significant at the 5% level). Despite this non-significant trend, patients treated with acamprosate had significantly more abstinent days, which was also confirmed by the period after the last relapse. These results support the ability of acamprosate to prevent relapse.

There were no significant differences between the treatment groups in craving intensity. A partial explanation for this might be the lack of sensitivity of the analogue craving scale.

One of the most vexing problems in treating alcoholics is the rapid drop-out rate (Baekeland *et al*., 1973). In our study, a particular problem of early differential attrition occurred in that seven patients from the acamprosate group and one from the placebo group dropped out after the first visit and before any follow-up data beyond baseline could be collected. In the absence of any follow-up data or confirmation of whether they took any study medication, these patients were therefore excluded from the ITT analysis. The method of excluding patients without any meaningful data beyond baseline from the ITT analysis is well accepted in the literature (Lehert, 1993) and certainly makes good sense. However, in this study, the differential attrition between the two groups introduces a weakness in the interpretation. If one speculates that these early drop-outs might have relapsed during the first week, this would have influenced the outcome of the study. At least, for

the survival analysis, measuring only first relapse, this would have reduced the difference between the two treatment groups. It is more difficult to speculate on possible influences on the CAD or SRD. This unexplained differential attrition therefore is a weakness in the outcome assessment of the study. However, after removing those individuals, baseline data collected suggested homogeneity in the two populations used for ITT analysis.

The CIWA scale is a physician rating scale measuring the severity of symptoms of acute withdrawal. In this study, the scale was rated on the first and seventh days of acute withdrawal, the two scheduled visits when the patient would see the physician during the first week. For both treatment groups, the mean scores dropped by 7.45 points on acamprosate and 7.04 points on placebo, with a difference which was not statistically significant. In retrospect, a weakness of the study protocol was that the CIWA was not scored more frequently during the first week, for example daily for the first 3 days and thereafter every second day. It is therefore not possible to conclude whether the rate of drop in CIWA score over 1 week differed between the two treatment groups. More frequent measures would not have been in keeping with the naturalistic approach of the protocol. Furthermore, the mean drop in score was ~10%, which appears to be rather small, suggesting that severe withdrawal symptoms at the beginning of detoxification were unusual.

Retrospective but detailed analysis was performed in search of a possible profile of patients that respond better than others on acamprosate. None of the baseline criteria identified acamprosate responders. The outcome of this analysis suggests that all patients with alcohol dependence remain possible candidates for treatment with acamprosate. The lack of responder profile published until now may suggest that identification of responders might require a different methodology, and may imply that the complex nature of alcohol dependence and its treatment still escapes adequate measurement of all dimensions.

In conclusion, our results show that acamprosate can be used from the beginning of the withdrawal phase without any unfavourable interaction with acute withdrawal medication, even though our design did not allow us to conclude whether this is a better option than starting after detoxification. Further research focusing on measurement of drug effect during the acute withdrawal phase remains an important objective for the future.

Acknowledgements — The participating investigators were Drs J. Guardia, A. Soler Insa, A. Mengual, J. Sanahuja (Barcelona), C. Carbonell, F. Montañes, N. Vicente, B. Rios (Madrid), M. A. Torres (Valencia), B. S. Pérez Galvez (Alicante), F. Reina, D. Martín (Sevilla), M. A. Lorenzo, A. Rodriguez (La Coruña), B. Bombín (Valladolid), J. Ogando, J. García, J. Fernandez (Bilbao). Merck Lipha Spain sponsored the study.

REFERENCES

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders, DSM III* 3rd edn, revised. American Psychiatric Association, Washington, D.C.

Aubin, H. J., Lehert, P., Beaupere, B., Jacquemin, F. and Barrucand, D. (1994) Tolérance de l'acamprosate aux médicaments du sevrage d'alcool. Essai multicentrique sur 591 alcooliques en sevrage. *Alcoologie* **16**, 32–41

Baekeland, F., Lundwall, L. and Shanahan, T. J. (1973) Correlates of patient attrition in the outpatient treatment of alcoholism. *Journal of Nervous and Mental Diseases* **157**, 99–107.

Chick, J. and Erickson, C. K. (1996) Conference summary: consensus conference on alcohol dependence and the role of pharmacotherapy in its treatment. *Alcoholism: Clinical and Experimental Research* **20**, 391–402.

Lehert, P. (1993) Review and discussion of statistical analysis of controlled clinical trials in alcoholism. *Alcohol and Alcoholism* **41** (Suppl. 2), 157–163.

Littleton, J. (1995) Acamprosate in alcohol dependence: how does it work? *Addiction* **90**, 1179–1188.

Mitchell, C., Simpson, D. and Chick, J. (1997) Carbohydrate deficient transferrin in detecting relapse in alcohol dependence. *Drug and Alcohol Dependence* **48**, 97–103.

Naassila, M., Hammoumi, S., Legrand, E., Durbin, P. and Daoust, M. (1998) Mechanism of action of acamprosate. Part 1. Characterization of spermidine-sensitive acamprosate binding site in rat brain. *Alcoholism: Clinical and Experimental Research* **22**, 1–8.

Paille, F., Guelfi, J. D., Perkins, A. C., Royer, R. J., Steru, L. and Parot, P. (1995) Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. *Alcohol and Alcoholism* **30**, 239–247.

Poldrugo, F. (1997) Acamprosate treatment in a long-term community-based alcohol rehabilitation programme. *Addiction* **92**, 1537–1546.

Potgieter, A. and Lehert, P. (1996) Acamprosate clinical trials: methodological considerations for assessment of drinking behavior. *1st Campral Symposium*, Soyka, M. ed., pp. 121–132. Springer, Berlin.

Quade, D. (1967) Rank analysis of covariance. *Journal of the American Statistical Association* **62**, 1187–1200.

Saivin, S., Hulot, T., Chabac, S., Potgieter, A. S., Durbin, P. and Houin, G. (1998) Clinical pharmacokinetics of acamprosate. *Clinical Pharmacokinetics* **35**, 331–345.

Sass, H., Soyka, M., Mann, K. and Zieglgänsberger, W. (1996) Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. *Archives of General Psychiatry* **53**, 673–680.

Selzer, M. L. (1971) The Michigan Alcoholism Screening Test: the quest of a new diagnostic instrument. *American Journal of Psychiatry* **127**, 1653–1658.

Sullivan, J. T., Sykora, K. and Schneiderman, J. (1987) Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British Journal of Addiction* **84**, 135–139.

Whitworth, A., Fischer, F., Lesch, O. M., Nimmerrichter, A., Oberbauer, H., Platz, T., Potgieter, A., Walter, H. and Fleishhacker, W. W. (1996) Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. *Lancet* **347**, 1438–1442.

Zeise, M. L., Kasparov, S., Capogna, M. and Zieglgänsberger, W. (1993) Acamprosate (calcium acetylhomotaurinate) decreases postsynaptic potentials in the rat neocortex: possible involvement of excitatory amino acids receptors. *European Journal of Pharmacology* **231**, 47–52.