

ACAMPROSATE AND RELAPSE PREVENTION IN THE TREATMENT OF ALCOHOL DEPENDENCE: A PLACEBO-CONTROLLED STUDY

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Abstract — The objective of this study was to compare acamprosate with placebo in the treatment of alcohol-dependent patients during a 6-month post-detoxification treatment and a 3-month medication-free follow-up. Patients ($n = 330$) were detoxified and randomized to treatment with acamprosate (1998 mg/day) or placebo within an out-patient programme including medical counselling, psychotherapy and self-help groups. The main outcome criterion was drinking behaviour as assessed by: abstinence/relapse ratio, cumulative abstinence duration (CAD) and the period of continued abstinence. Anxiety, depression and craving were also monitored. Intention to treat (ITT) statistical principles were followed. Twenty-five per cent of patients dropped out over the first 6 months. At the end of the treatment period, the abstinence rate was 57.9% for acamprosate and 45.2% for placebo ($P = 0.03$). The CAD was 110 ± 77 days for acamprosate and 89 ± 77 days for placebo ($P = 0.016$). Patients on acamprosate had a higher continuous abstinence rate and experienced less severe relapses. No differential effect was noted for anxiety, depression or craving. Treatment remained positive, but not significant, 3 months after termination of study medication. No significant difference in adverse events was noted between treatment groups. Acamprosate treatment over 180 days was consistently more effective than placebo to maintain abstinence and to diminish relapse severity.

INTRODUCTION

Relapse prevention is a major challenge in the treatment of alcoholism. About 50% of detoxified alcoholics relapse within 3 months (Miller and Hester, 1986). The observation that craving for alcohol and compulsion to drink are frequent causes of early relapse has led to the search for pharmacological treatments to reduce craving and to modulate alcohol-oriented behaviour in post-detoxification programmes.

Acamprosate (calcium acetylhomotaurinate) is an analogue of amino acid neurotransmitters such as taurine and homocysteic acid and is reported to exert anti-excitatory amino acid properties (Zeise *et al.*, 1993). Most placebo-controlled clinical trials with acamprosate in detoxified alcoholics demonstrated statistically significant decreases in relapse in patients treated with acamprosate. In three short-term studies (3 months) without follow-up, the number of relapses at the end of treatment was statistically significantly lower in patients treated with acamprosate (Hillemand *et al.*, 1984–1985; Gerra *et al.*, 1992; Pelc *et al.*, 1997). In another 3-month study, only differences in laboratory markers such as γ -glutamyl transpeptidase (GGT) levels could be demonstrated, without control for pre-trial levels (Lhuintre *et al.*, 1990). In the intermediate to long-term studies (6–24 months) which included follow-up periods without medication, continuous abstinence and the cumulative duration of abstinence were usually the main endpoints for analysis (Paille *et al.*, 1995; Pelc *et al.*, 1996; Sass *et al.*, 1996; Whitworth *et al.*, 1996; Poldrugo, 1997). The main outcome criteria were time to first relapse and continuous abstinence rates (patients never drinking throughout the total duration of the study), the cumulative number of abstinent days during the study period (cumulative abstinence duration) and relapse

frequencies at every visit. Patients on acamprosate had significantly better outcome than patients on placebo in all these studies.

The present double-blind, placebo-controlled trial was aimed at comparing acamprosate with placebo in alcohol-dependent subjects undergoing a comprehensive post-detoxification programme of 6 months of treatment and 3 months of drug-free follow-up, in the southern part of Italy, known for high *per capita* and daily wine consumption. Unlike most previously published studies, alcohol-dependent patients in this study were not only recruited from psychiatric departments and addiction units, but the majority from general medical and neurological departments.

SUBJECTS AND METHODS

The design was a multicentre double-blind placebo-controlled study in which 18 out-patient centres in Italy participated (11 internal medicine or neurology units, four addiction units and three psychiatry units). The study duration was 9 months, during which the patients received study medication for the first 6 months (two 333 mg tablets of acamprosate three times per day or equivalent placebo), and were followed up without medication for the subsequent 3 months. All centres adopted an integrated treatment approach to alcoholism, in which a post-detoxification programme included pharmacotherapy and weekly medical counselling on alcohol-related problems. Individual behaviour-oriented supportive counselling (1–2 sessions/week, 1 h per session) and Alcoholics Anonymous (AA) attendance (2–3 times/week) were available to all patients who wanted to participate in them for the 6-month treatment period of the study. The study protocol was submitted to and approved by the local ethics committees. Written informed consent was obtained from each patient.

Subjects

Three hundred and forty patients aged between 18 and 65 years, diagnosed as alcohol-dependent according to

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DSM-III-R criteria (American Psychiatric Association, 1987), were screened (DSM-IV was not validated in Italian when the study was conducted). They had to have γ -glutamyltransferase (GGT) values at least twice the upper limit of normal and/or a mean corpuscular volume (MCV) of 95 fl or higher; agree to receive alcohol weaning therapy in order to be abstinent for at least 5 days before entering the study; and have at least a 12-month history of alcohol dependence.

Exclusion criteria were: pregnancy, psychiatric disorders that required specific drug treatment or interfered with assessment, epilepsy unrelated to alcoholism, cardiac or renal failure, hypercalcaemia, hyperparathyroidism, neoplasm, cholelithiasis, poorly controlled diabetes, pernicious anaemia, and decompensated liver disease. Patients in post-treatment centres, without established residence, and without known spouses or relatives able to supply information on the post-detoxification outcome were also excluded.

Procedure and assessments

Of the 340 patients screened, 10 did not comply with inclusion criteria and 330 were randomized, by sealed envelope with balance by blocks of eight, to 180-day treatment with acamprosate (1998 mg/day for 164 patients) or placebo (166 patients). They received two tablets of acamprosate (2×333 mg) or the identical placebo equivalent three times daily to be taken during meals. Patient progress was recorded monthly during the 6 months of treatment, and thereafter twice with 6-week intervals during a 3-month follow-up period. If patients required 2 weeks or more hospitalization for relapse during the study, they were withdrawn from the study.

Baseline assessments included demographic data, history of drinking pattern (duration of alcoholism, previous treatments etc.), family and medical history, CAGE questionnaire (Ewing, 1984) and Michigan Alcoholism Screening Test (MAST) (Selzer, 1971).

Continuous assessments included alcohol consumption, 10 cm visual analogue scale for craving, Hamilton Depression (Hamilton, 1967) and Anxiety (Hamilton, 1959) Scales, psychosocial adaptation (score range: 0–3 measured for socio-familial and work environment dimensions), dependence severity according to DSM-III-R (mild, moderate, severe), hand, mouth or tongue tremors (absence of, mild, moderate, severe), Clinical Global Impression (CGI) (Guy, 1996) and laboratory examinations including GGT, aspartate (AST) and alanine (ALT) aminotransferase levels, full blood count (FBC), urea nitrogen and electrolytes. Adverse events were recorded by spontaneous reporting and by a questionnaire listing 45 events.

Drinking behaviour

Drinking behaviour was the main outcome criterion: as principal assessment, abstinence or relapse for each period between assessment visits, cumulative abstinence duration (CAD) and uninterrupted (continued) abstinence. Relapse was defined as any alcohol consumption. As a secondary endpoint, relapse severity was measured.

Abstinence rate. Abstinence/relapse declaration at each visit reflected drinking behaviour from the previous visit to the assessment time. When no information about patients not attending examinations could be obtained, the 'worst scenario' hypothesis was followed and such patients were considered as

relapsing at that time. A success/failure index was calculated (Mantel–Hänszel test): since the protocol required a minimum treatment period of 6 months, patients who were lost to follow-up were considered as treatment failures together with those who had a relapse. Only those who abstained were regarded as treatment success.

Cumulative abstinence duration. CAD was defined as the number of days of abstinence during the treatment period (Lehert, 1993). Due to uncertainty regarding accurate reporting of duration of relapses, if a relapse was recorded at a visit, the entire month before the visit was considered as a period of relapse, irrespective of the declared duration of the relapse.

The time to first relapse. The period of continued abstinence was calculated by using a survival analysis. The occurrence of the first relapse, regardless of possible later recovery, was considered as treatment failure (missing data on drinking behaviour were also considered as relapse). Only uninterrupted abstinence throughout the entire treatment period was considered as ultimate success for this analysis. In the absence of a detailed patient's diary, we took the mid-point of the treatment period in which the event occurred as the date of relapse.

Relapse severity. The frequency and amount of alcohol consumed per day were measured for those patients who had relapsed. Based on patient report at each visit, the consumption frequency was recorded as: 0, abstinence; 1, up to 2 days per week; 2, 3–6 days per week; 3, every day of the week; the quantity of alcohol consumed was recorded as: 0, abstinence; 1, <5 drinks per day; 2, 5–10 drinks/day; 3, >10 drinks per day (one drink/unit was considered the equivalent of 1 glass of wine, $\frac{1}{2}$ pint of beer or 1 measure of spirits). Mean scores were calculated for graphic representation.

Statistical analysis

Statistical analysis (significance level: 5%) followed the intention to treat (ITT) principle and the 'worst scenario' hypothesis for missing patients (Gillings and Koch, 1991). Any randomized patient who took at least one dose of the trial medication was eligible for analysis (Pattison, 1979). Baseline and outcome data from both groups were compared by the χ^2 (percentage data) and *t*-tests (mean \pm SD). The success/failure index difference was evaluated by the Mantel–Hänszel test. The Kaplan–Meier survival analysis was employed in order to measure continued abstinence, and the comparison between the median periods of abstinence was performed by means of the Lee–Desu statistics. Other outcome data (see above) were analysed by the Cochran test for repeated dichotomous measurements. To assess the possible influence of other factors on CAD, multifactorial and multiple regression analyses were performed, using age, gender, trembling, psychological adaptation, family history, psychotherapeutic support, AA attendance, psychological and physical dependence, CAGE score, MAST score and Hamilton anxiety and depression scores as variables.

RESULTS

Baseline

The baseline characteristics of both acamprosate- and placebo-treated patients are summarized in Table 1. There were no statistically significant differences between the groups

Table 1. Baseline data

	Treatment					
	Acamprosate <i>n</i> = 164		Placebo <i>n</i> = 166		Total sample <i>n</i> = 330	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	45.87	11.33	46.01	11.09	45.94	11.19
Drinking history (years)	11.08	9.86	10.25	7.97	10.66	8.93
Total MAST score	22.23	10.59	23.24	10.68	22.74	10.63
GGT (IU/l)	205.75	206.15	216.41	260.91	211.11	235.00
MCV (fl)	100.10	4.43	99.60	3.64	99.85	4.05
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Sex						
Female	25	(15.2)	32	(19.3)	57	(17.3)
Marital status						
Married	111	(67.7)	114	(68.7)	225	(68.2)
Unmarried	37	(22.6)	31	(18.7)	68	(20.6)
Divorced	2	(1.2)	8	(4.8)	10	(3.0)
Widowed	14	(8.5)	13	(7.8)	27	(8.2)
Consumption awareness	129	(78.7)	147	(88.6)	276	(83.6)*
Previous treatment for alcoholism	11	(6.7)	22	(13.3)	33	(10.0)*
Alcohol amount						
≤5 drinks/day	6	(3.7)	9	(5.4)	15	(4.5)
5–10 drinks/day	68	(41.5)	72	(43.4)	140	(42.4)
>10 drinks/day	90	(54.9)	85	(51.2)	175	(53.0)
Alcohol frequency						
≤2 days/week	4	(2.4)	2	(1.2)	6	(1.8)
3–6 days/week	19	(11.6)	24	(14.5)	43	(13.0)
Daily	141	(86.0)	140	(84.3)	281	(85.2)
Total	164	(100.0)	166	(100.0)	330	(100.0)

**P* < 0.05.MAST, Michigan Alcoholism Screening Test; GGT, γ -glutamyltransferase; MCV, mean corpuscular volume.

with respect to demographic parameters. For criteria related to alcoholism, the two groups were similar, except that more patients in the placebo group recorded positive answers to a question whether they were aware of their excessive alcohol consumption and they had more commonly had treatment for alcohol problems in the past.

Outcome

Two-hundred-and-forty-six patients completed the 180-day treatment period. Less than 25% of patients withdrew during the treatment phase. Attrition was equal in both treatment groups: 40 patients (24.4%) on acamprosate and 44 patients (26.4%) on placebo (Table 2). To record the reasons for withdrawal, the investigators allocated a termination status code to all patients (Table 2). Two withdrawals occurred due to adverse events (lower limb oedema in two females with chronic alcoholism). Twenty-two patients (11 in each treatment group) were re-hospitalized more than 14 days for severe relapses, which, according to the study protocol necessitated withdrawal from the study.

Abstinence rate. The rate of abstinence, relapses and withdrawals at each visit is reported in Table 3. A difference in favour of the acamprosate group was seen from day 30 onwards, but only became statistically significant (*P* < 0.05) at the 150- and 180-day visits. The success/failure ratios based on such data revealed statistically significant differences in favour of acamprosate at all visits after baseline, except at day 120.

Table 2. Reasons for study drop-outs

Termination status	Acamprosate <i>n</i> = 164		Placebo <i>n</i> = 166		Total <i>n</i> = 330	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Adverse events	2	1.2	0	–	2	0.6
Rehospitalization for severe relapse	11	6.7	11	6.6	22	6.7
Lost to follow-up	16	9.8	15	9	31	9.4
Patient's refusal or inability to continue	9	5.5	16	9.6	25	7.6
Bad compliance	2	1.2	2	1.2	4	1.2
Sub-total of drop-outs	40	24.4	44	26.4	84	25.5

Cumulative abstinence duration. The CAD over the treatment period of 180 days showed a significantly (*P* = 0.016) longer duration of abstinence in the acamprosate-treated patients (110 ± 77 days) than in the placebo group (89 ± 77 days). A multifactorial analysis of the influence of baseline patient characteristics on CAD suggested that treatment significantly determined CAD in seven out of 16 measured variables, whereas the co-factor only determined CAD for three variables (see Table 4). No interaction between the treatment and the co-factors could be demonstrated.

The time to first relapse. The cumulative chance for patients to remain abstinent after withdrawal was significantly higher for patients receiving acamprosate than for those receiving

Table 3. Frequency of abstinence, relapse and drop-outs at each assessment interval

Day	Acamprosate <i>n</i> = 164						Placebo <i>n</i> = 166						χ^2 ^a <i>P</i>	Mantel– Hänszel ^b <i>P</i>
	Abstinent		Relapse		Drop-outs		Abstinent		Relapse		Drop-outs			
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)		
0	163	(99.3)	1	(0.6)	0	(–)	166	(100)	0	(–)	0	(–)	0.31	0.31
30	112	(68.3)	48	(29.3)	4	(2.4)	93	(56)	64	(38.6)	9	(5.4)	0.05	0.02 ^b
60	106	(64.6)	37	(22.6)	21	(12.8)	89	(53.6)	53	(31.9)	24	(14.5)	0.10	0.04 ^b
90	96	(58.5)	41	(25.0)	27	(16.5)	79	(47.6)	57	(34.3)	30	(18.1)	0.11	0.04 ^b
120	95	(57.9)	31	(18.9)	38	(23.2)	81	(48.8)	46	(27.7)	39	(23.5)	0.13	0.09
150	96	(58.5)	29	(17.7)	39	(23.8)	77	(46.4)	49	(29.5)	40	(24.1)	0.02 ^a	0.02 ^b
180	95	(57.9)	29	(17.7)	40	(24.4)	75	(45.2)	47	(28.3)	44	(26.5)	0.03 ^a	0.02 ^b

^aComparison of abstinence and relapse.

^bComparison of success/failure ratio.

Table 4. Multifactorial analysis of cumulative abstinence duration

Factor	<i>F</i> value		
	Factor (<i>P</i>)	Treatment (<i>P</i>)	Interaction (<i>P</i>)
Age	2.09 (0.082)	4.04 (0.045)	0.66 (0.618)
Sex	1.57 (0.211)	0.80 (0.371)	1.41 (0.237)
Trembling	2.74 (0.099)	4.81 (0.029)	1.37 (0.243)
Psychological adaptation	0.54 (0.657)	8.16 (0.005)	2.28 (0.079)
Familial history	4.51 (0.034)	5.20 (0.023)	0.01 (0.929)
Psychotherapy support	1.39 (0.239)	2.34 (0.127)	0.08 (0.775)
AA group attendance	2.96 (0.086)	2.87 (0.091)	0.00 (0.985)
Psychological dependence	2.29 (0.079)	0.94 (0.332)	0.32 (0.812)
Physical dependence	2.81 (0.039)	0.03 (0.856)	0.61 (0.609)
CAGE item I	0.05 (0.821)	0.14 (0.705)	1.50 (0.221)
CAGE item II	2.57 (0.110)	1.95 (0.163)	0.08 (0.776)
CAGE item III	0.81 (0.370)	4.98 (0.026)	0.35 (0.552)
CAGE item IV	0.02 (0.890)	3.05 (0.082)	0.22 (0.641)
MAST total score	1.18 (0.317)	5.36 (0.021)	0.27 (0.848)
Anxiety total score	2.18 (0.090)	3.86 (0.050)	0.65 (0.583)
Depression total score	3.87 (0.010)	3.91 (0.049)	0.10 (0.958)

placebo and the difference between the groups increased slightly during the treatment period (Fig. 1). The median time of abstinence prior to the first relapse was significantly ($P < 0.01$) longer with acamprosate (135 days) than with placebo (58 days). More patients on acamprosate (48%) remained continuously abstinent during the 6-month treatment, than patients on placebo (33%, $P < 0.01$). These percentages dropped respectively to 38% and 29% after the additional 3-month follow-up without study medication.

Quantity and frequency of relapse. Figure 2a and b shows respectively the mean score of the frequency and quantity of alcohol consumption during periods of relapse. Only patients who relapsed at each time point were taken into consideration for this analysis (see Table 3). During the active treatment period patients in the acamprosate group had slightly less frequent drinking episodes and consumed less alcohol during relapses than patients on placebo. Although from a clinical point of view the differences appeared to be small, they were statistically significant at several time points. Quantity of consumption was significantly less at all assessments, except those on days 90 and 120 and for frequency at all assessments, except on day 120. Although the difference between groups remained statistically significant until the end of the treatment, there was no significant difference in the medication-free follow-up period.

Other outcome criteria

For both treatment groups, severity of dependence, tremors, psychosocial adaptation, craving and depression all significantly ($P < 0.001$) improved during the treatment period. However, no significant difference between the two groups was found for these variables (data not shown).

Attendance of the proposed psychotherapy programme and of AA self-help groups varied during the course of the study. Over the treatment period 24–38% of patients participated in the AA programmes and 18–28% of patients attended psychotherapy sessions, without statistically significant differences between the two medication groups. Approximately half of the patients who attended AA also participated in psychotherapy sessions and two thirds of patients who participated in psychotherapy sessions also attended AA. At any visit, 55–58% of patients did not attend either of these.

Compliance

Compliance was measured by tablet count from the returned containers and by assessment of the investigator, as 'regular intake', 'occasional non-compliance' or 'tablets never taken'. Compliance between the two treatment groups was without any significant difference. The mean number of tablets returned varied between 8.8 ± 18.5 and 11.7 ± 22.3 at the

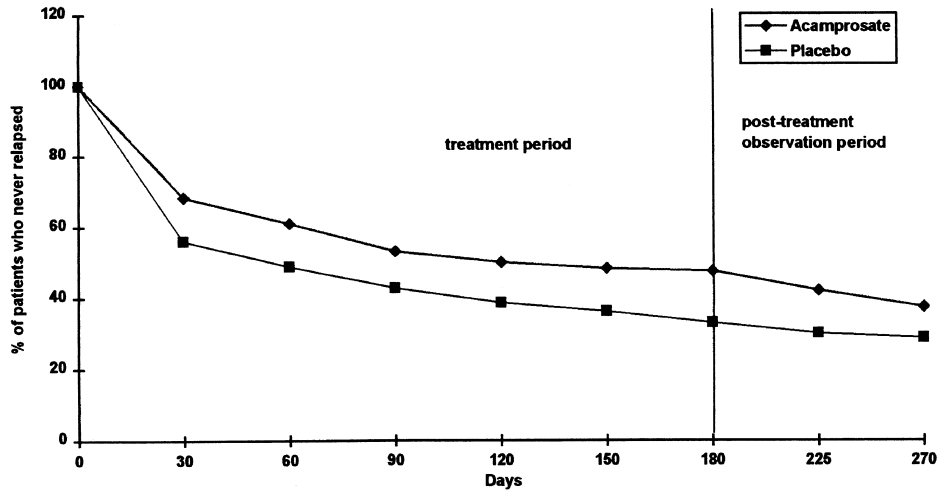


Fig. 1. Mean cumulative chance to remain abstinent after withdrawal (survival analysis to first relapse). Lee–Desu statistics: $P < 0.01$.

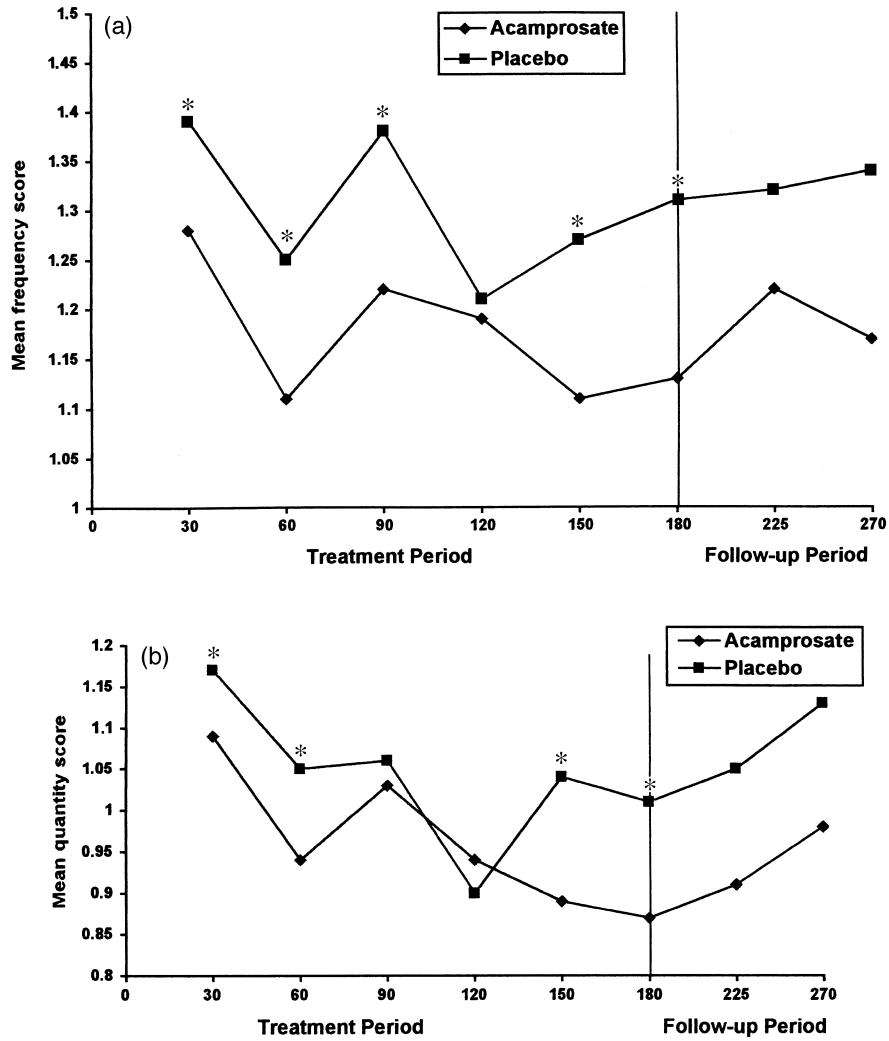


Fig. 2. (a) Frequency of alcohol consumption in patients who relapsed. Frequency score: 0, no drinking; 1, up to twice/week; 2, 3–6 times per week; 3, every day of the week. $*P < 0.05$.
 (b) Quantity of alcohol consumption in patients who relapsed. Quantity score: 0, no drinking; 1, up to 5 drinks; 2, 5–10 drinks; 3, >10 drinks/day. $*P < 0.05$.

respective visits, which suggests a good compliance. Between 76.9% and 84.5% of patients were considered to have had 'regular intake' of study medication.

Adverse events

Any spontaneously reported adverse event was recorded and a checklist of 45 potential symptoms was filled out at every visit to detect events not spontaneously reported. The checklist frequencies were consistently higher than spontaneous reports and are accordingly reported here. The most common adverse event was headache (7.3% of patients in the acamprosate group and 6.6% in the placebo group). Diarrhoea was reported in 3.0% (acamprosate) and 2.4% (placebo) and epigastric discomfort in 1.2% (acamprosate) and 5.6% (placebo) of patients respectively. None of the events recorded showed any significant difference between the two treatment groups. The frequency of adverse events diminished over the study period. In the acamprosate group, a total of two patients (both females) withdrew from treatment after reporting oedema of the lower legs after drug exposures of a few days and 1 month respectively. A total of three patients on acamprosate and one on placebo reported lower limb oedema. Since oedema is a known symptom in chronic alcoholism, this was not considered as related to the study medication. One patient complained of severe pruritis 2 days after he started acamprosate treatment. He continued taking the medication and, although the pruritis remained, it became less intense.

Follow-up period

Of the 246 patients who completed the double blind treatment, 234 (95%) entered and completed the 90-day observation period without study medication. During this period, the proportion of abstinence in the acamprosate group remained superior to placebo, but the difference between the two groups gradually decreased (49% abstinence on acamprosate and 41% on placebo at the end of the period) with no statistically significant difference between treatment groups at the end of the follow-up ($P = 0.154$). CAD over the entire study period of 270 days remained significantly higher on acamprosate, compared with placebo (155 ± 114 days on acamprosate and 127 ± 115 days on placebo, $P = 0.028$). No signs of drug withdrawal after abrupt termination of study medication were recorded.

DISCUSSION

The results of this study confirm the efficacy of acamprosate to maintain abstinence in alcohol-dependent patients and support the results of previously published studies (Paille *et al.*, 1995; Pelc *et al.*, 1996; Sass *et al.*, 1996; Whitworth *et al.*, 1996; Poldrugo, 1997). Relapse rates were significantly lower (10–12%) in patients treated with acamprosate than in those treated with placebo. The median time to the first relapse was 77 days longer with acamprosate than with placebo treatment, and after the 6-month treatment, 48% of acamprosate-treated patients never had a relapse, compared to 33% of the placebo-treated patients. The duration of abstinence (mean CAD) was 21 days longer in the acamprosate group and the drug was well tolerated by patients. The follow-up data at the end of the 90-day treatment-free period confirmed that the

outcome was still in favour of acamprosate-treated patients, although no longer statistically significant. The smaller difference between treatment groups during the follow-up period could suggest that some patients may have benefited from acamprosate treatment for longer than 6 months.

One possible weakness is the statistical difference between the two treatment groups for two criteria at baseline: the placebo group had more commonly had treatment for alcohol problems in the past, which may disadvantage the prognosis for treatment (Pettinati *et al.*, 1996), but also declared more 'awareness' of their alcohol problem, which on the other hand may have favoured the prognosis (although this was only measured by one question asking whether they were aware of their alcohol problem). Whether these two factors may have balanced each other out is not certain. These possible biasing factors may have influenced the outcome of the study.

Despite similarities with previously published studies, more detailed comparison revealed some interesting differences. Over the same treatment period, Poldrugo (1997) obtained abstinence rates of 48% on acamprosate and 32% on placebo, Pelc *et al.* (1996) obtained abstinence rates of 33% on acamprosate and 9% on placebo and Paille *et al.* (1995) obtained abstinence rates of 44% on acamprosate and 30% on placebo after 6 months, compared to the abstinence rates in our study of 58% on acamprosate and 45% on placebo. The abstinence rates in our study were higher in both treatment groups, but the difference between the two treatment groups seemed less. This suggests a more prominent placebo or supportive treatment effect in our study, which could to some extent have contributed to mask some of the drug effect. In our study, patients were also assessed monthly, which is more frequent than in some of the previously reported acamprosate studies mentioned above, which assessed patients with 6–12 week intervals towards the end of the treatment period (e.g. Pelc *et al.*, 1996; Sass *et al.*, 1996). This may also have had an influence on the outcome by potentially providing more counselling opportunities for patients. The duration of abstinence (CAD) in our study was 110 ± 77 days on acamprosate and 89 ± 77 days on placebo, compared to 99 ± 79 days and 70 ± 74 days respectively in the Poldrugo (1997) study and 60 ± 21 days and 49 ± 15 days respectively in the Pelc *et al.* (1996) study. The median time to the first relapse in our study was 135 days on acamprosate and 59 days on placebo, compared to 150 days and 60 days respectively in the Poldrugo study. However, it is important to note that CAD and time to first relapse were estimated according to preset assumptions and should not be regarded as precise measures.

Another difference between our study and those previously published seems to be the higher patient retention rates we recorded: 76% of patients in the acamprosate group and 74% in the placebo group were retained in the study after 6 months of treatment, and we found a 71% overall retention after a further 3-month follow-up without treatment. Over a 6-month study treatment duration, Poldrugo (1997) reported retention rates of 53% for acamprosate- and 38% for placebo-treated patients, Pelc *et al.* (1996) reported 44% for acamprosate and 22% for placebo patients, and Paille *et al.* (1995) found retention rates of 71 and 53% respectively after 6 months.

The reason for the higher retention rate in our study is not clear. One apparent difference between our study and the other published studies seems to be that the majority of our patients

(59%) were recruited from medical and neurological centres treating physical, rather than psychiatric or addictive, problems, unlike the other published studies in which patients seem to have been recruited mainly or only from psychiatric and addiction centres. Whether the patients in our study had less troublesome psychiatric, emotional or social disturbances is not certain, but should be considered.

A further important difference in our study was that we did not have any noticeable differential attrition between treatment groups, as was described by most of the above-mentioned studies, and which Sass *et al.* (1996) considered as an interesting but complicating factor in interpreting the results. This suggests that both treatment groups had equal exposure to supportive counselling and therefore our study measured treatment effect without retention difference. Our results therefore seem to confirm that acamprosate has a relapse prevention effect independent of retention effect. The positive retention effect which manifested itself in other studies appears to have enhanced the efficacy, as for example in the study by Poldrugo (1997), which had a 16% difference in abstinence rate between acamprosate and placebo groups and the Pelc (1996) study, which had a 24% difference between treatment groups, compared to the 12% difference in our study over the same treatment period. It cannot be excluded that, with less care given toward patient retention in our centres, similar effects might be experienced under more naturalistic/less experimental conditions of treatment.

As for previous studies with acamprosate, absolute abstinence was the primary goal in our study. Nevertheless, as a secondary endpoint, the quantity and frequency of alcohol intake were also measured in those patients who failed to remain abstinent. The difference in the quantity and the frequency of alcohol consumption between the treatment groups seemed relatively small from a clinical point of view. Nevertheless, the fact that they proved to be statistically significant in favour of the patients on acamprosate for most of the active treatment period suggests more control over alcohol consumption in those patients who do not succeed in abstaining, and this possibility needs to be further examined in future studies.

The possible weaknesses in the study design include the following: (1) The psychosocial support was not standardized and not all patients chose to participate in these supportive programmes. Although this theoretically improves the external validity of the results, it complicates interpretation of the data. On the other hand the exclusion of patients without cooperative relatives may have reduced the generalizability of the results. (2) The approximation to estimate CAD overestimates periods of relapse, which may exaggerate the difference between the treatment groups. More reliable information on relapse would have been preferable. (3) The possibility of un-blinding as a result of differential adverse events in this study seems remote, but particular testing for blinding was not performed.

One of the main actions of acamprosate appears to be the reduction of neuronal hyperexcitability associated with excitatory amino acid receptor activation (Zeise *et al.*, 1993). It has been hypothesized that the drug's clinical efficacy may therefore consist of inhibition of negative aspects of craving, such as anxiety (Emrick *et al.*, 1993). The Hamilton anxiety and VAS craving scores in this study decreased to the same extent in the two treatment groups during treatment, and could not confirm this hypothesis. However, it is also possible that

their sensitivity and specificity were not sufficient to detect possible changes in negative reinforcement.

In the majority of studies published to date, acamprosate reduced drinking but there was no conclusive evidence from visual analogue scale measurements that it attenuated craving (Lhuintre *et al.*, 1990; Gerra *et al.*, 1992; Paille *et al.*, 1995; Pelc *et al.*, 1996, 1997), which seems consistent with our findings. Therefore the authors suggest that the possible anti-compulsive effect of the product, which is controlling drinking behaviour even in the presence of craving, rather than a specific anticraving effect, should also be considered in future research. In agreement with Littleton (1995), we suggest that newly designed instruments are needed to evaluate anti-craving and anti-compulsive mechanisms of drugs in clinical settings (Emrick *et al.*, 1993). The obsessive-compulsive drinking scale (Anton *et al.*, 1996) may be one instrument to assess possible change in compulsive drinking tendencies in patients treated with acamprosate.

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