UNITED KINGDOM MULTICENTRE ACAMPROSATE STUDY (UKMAS): A 6-MONTH PROSPECTIVE STUDY OF ACAMPROSATE VERSUS PLACEBO IN PREVENTING RELAPSE AFTER WITHDRAWAL FROM ALCOHOL

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Abstract — A 6-month randomized controlled study of acamprosate versus placebo in preventing relapse following withdrawal from alcohol was undertaken in 20 centres throughout the UK. Patients diagnosed as alcohol-dependent and detoxified within the preceding 5 weeks were randomly assigned to treatment with either acamprosate (A) 666 mg three times/day or identical placebo (P). A total of 664 patients were screened; 581 were entered into the treatment phase. One-third were episodic drinkers, 84% were male, 44% were unmarried and 48% were unemployed. Medication was first taken on average 24 days after the start of detoxification; 32% of patients had already relapsed by this time. The 6-month study period was completed by 35% of patients; adverse events led to withdrawal of a further 14% (A) and 9% (P) respectively. Compliance was poor in that, by the end of the second week, only 57% of patients were judged to be taking at least 90% of their tablets. The mean total of abstinent days achieved was 77 (A) and 81 (P). Complete abstinence for 6 months was achieved by 12% (A) and 11% (P); drinking remained within controlled limits in a further 3% (A) and 6% (P). An effect of acamprosate on consumption was not seen when subgroups, including those defined by the Lesch typology, were analysed separately. However, the mean percentage reduction in craving for alcohol measured on a visual analogue scale was greater in the acamprosate, than placebo, patients at week 2 and week 4 (P < 0.001) and the mean decrease in the Hamilton Anxiety score at the 4th week was greater in the acamprosate than placebo patients (P = 0.017). In comparison with other published trials of acamprosate, patients started study medication after a longer time following detoxification, had more often recommenced drinking before medication was started and had a higher drop-out rate, and this might have contributed to the lack of a treatment effect in this study.

INTRODUCTION

The rapidity of relapse in alcohol-dependent patients who have sought assistance to withdraw from alcohol is a cause for concern. Admissions of patients diagnosed as alcohol-dependent is placing an increasing burden on acute medical services (Chick, 1997). Advances in understanding the neuropharmacology of alcohol dependence and the rapid reinstatement of the syndrome after abstinence have supported hopes that pharmacotherapy may aid recovery (Chick and Erickson, 1996).

There is evidence that acamprosate, calcium acetyl homotaurinate, can lengthen time to relapse, reduce drinking days, and increase the percentage attaining complete abstinence among alcohol-dependent patients who have accepted treatment for their condition (see e.g. Sass et al., 1996; Whitworth et al., 1996; Geerlings et al., 1997; Pelc et al., 1997; Poldrugo, 1997). Homotaurinate is a naturally occurring structural analogue of γ-aminobutyric acid (GABA); acamprosate is a synthetic derivative. This compound crosses the blood–brain barrier, modulates GABA transmission (Daoust et al., 1992), decreases postsynaptic potentials in the neocortex, perhaps by affecting excitatory amino acid (N-methyl-D-aspartate: NMDA) receptors (Zeise et al., 1993), and diminishes voluntary alcohol intake in alcohol-prefering rats (Boismare et al., 1984; Le Magnen et al., 1987a; Gewiss et al., 1991). Evidence by Lamblin et al. (1993), Rassnick et al. (1992) and other studies reviewed by Tsai et al. (1995) implicates glutamate neurotransmission, and NMDA modulation thereof, in the GABA system in alcohol-seeking behaviour. Tsai et al. (1998) assessed glutamatergic neurotransmission and oxidative status in alcohol-dependent patients after acute alcohol withdrawal and 4 weeks later and found persistent abnormalities in cerebrospinal fluid. Littleton (1995) has proposed that one of acamprosate’s actions, mediated by its effects on calcium channels as well as on the NMDA receptors in the glutamate system, is to suppress conditioned alcohol withdrawal craving.

Acamprosate administration to animals does not give rise to a dependence syndrome (Grant and Woolverton, 1989), nor does it exacerbate either acute or chronic ethanol toxicity in rats (Le Magnen, 1987b). When alcohol-dependent patients who have been abstinence while taking acamprosate cease taking the drug they do not experience a rebound of craving or alcohol misuse (Whitworth et al., 1996). The drug thus has no abuse potential.

This paper reports the results of the first study into the safety and efficacy of acamprosate in a sample of patients attending specialized treatment centres in the UK. Its design differed in some respects from previously reported trials, including its use of a diary card on which patients were to record on a daily basis any alcohol consumed instead of relying on memory at assessment visits. Some preliminary data from this study were previously published in Conference Proceedings (Soyka, 1996).

PATIENTS AND METHODS

Design

This work was undertaken in 20 UK clinics during 1991–1993 as a 6-month randomized controlled study of acamprosate versus an identically presented placebo. The clinics were connected with psychiatric services and a general hospital, including both teaching hospitals and district general hospitals. It was intended that the medication would be used
as an adjunct, not an alternative, to the clinic’s usual psychosocial out-patient treatment programme. No check on blindness of patients or assessors was made; in other ways this study design followed criteria recommended by Moncrieff and Drummond (1998) and the Plinius Maior Society (1994).

A recruitment examination and assessment was conducted within 5 weeks of the end of detoxification (defined as at least 5 days of abstinence). Detoxification may have been carried out on an in-patient or an out-patient basis. The length of this ‘pre-baseline period’, up to 5 weeks, was chosen, because some patients to be recruited would be undergoing in-patient treatment of about 4 weeks duration. There was then a ‘washout’ period of 1 week, during which patients had to be free of benzodiazepines and were instructed not to drink alcohol. Patients were then reassessed and, using randomization in blocks of eight, allocated to treatment with either active medication, acamprosate 1998 mg (two tablets of 333 mg each three times per day), or identically presented placebo (also two tablets three times per day). Assessments were made after 1 week on medication, then at 2-weekly intervals, and later at 4-weekly intervals for a total of 24 weeks. Medication was stopped and patients then reassessed 4 weeks later to monitor the effects of the abrupt withdrawal of the study medication. In all, 11 assessments were planned (see Fig. 1).

During the study, the protocol was amended to allow reduction of the dosage to four tablets per day if gastrointestinal side-effects were distressing. The study was approved by the local Ethics of Research Committee at each UKMAS centre.

Treatment for detoxification when on medication during the study, even if hospital admission were required, was not a reason for withdrawal from the study, nor was the prescription of benzodiazepines for periods up to 7 days. Admission to hospital for reasons other than alcohol withdrawal was regarded as a serious adverse event and led to withdrawal from the study. Benzodiazepines were not permitted for other purposes, but the urine checks made did not systematically include a check for these or other drugs.

### Inclusion and exclusion criteria

Patients were included if they were 18–65 years of age, weighed >60 kg (later modified to 50 kg), fulfilled criteria for alcohol dependence (DSM-III; American Psychiatric Association, 1980), had at least a 12-month history of alcohol dependence, had undertaken withdrawal from alcohol during the preceding 5 weeks, had been abstinent for at least 5 days before enrolment to the study and gave written informed consent.

Patients were excluded if they were receiving disulfiram or calcium carbimide, drugs known to induce hepatic enzymes with the exception of oral contraceptives, or tranquillizers on a regular basis. Patients were also excluded if they had abused drugs in the previous 12 months, had serious medical or psychiatric disorders, or were pregnant or at risk of becoming pregnant. During the study any patient given drugs known to induce hepatic enzymes or psychotropic medication, apart from hypnotics, were withdrawn from the study.

### Baseline measures

At baseline, a drinking history was obtained, and the following scales completed: the SADQ (Stockwell et al., 1983) in which a score of 30 suggests severe dependence (range 0–60), the MAST (Selzer, 1971) in which a score of 5 indicates ‘alcoholic’ (range 0–52) and the CAGE (Ewing, 1984) in which a score of 2 indicates a probable alcohol problem (range 0–4).

### Safety monitoring

Tolerance of the drug, concomitant diseases, concurrent medications, and vital signs were recorded at every visit; physical examination including ECG was conducted before and after the study, and blood samples for measurement of haematological and biochemical variables (analysed at a centralized laboratory) were taken at entry and after 1 month, 3 months and at the end of the medication period. At the visit immediately prior to starting medication, and at 1, 3 and 6 months, the clinician rated the Hamilton Anxiety and the
Hamilton Depression scales (Hamilton, 1959, 1967 respectively).

**Outcome variables**

**Indicators of alcohol consumption.** At each assessment, breath alcohol was checked using an alcolmeter (Lion Laboratories, Ty Verlon, Cardiff, UK); the patients rated their degree of craving on a visual analogue scale 100 mm long [no desire for alcohol (0 mm) to uncontrollable desire for alcohol (100 mm)]; a record card (Fig. 2) was issued on which patients were asked to note on a daily basis whether or not they drank and how much, and the previous period’s card was collected. At 1 month, 3 months and 6 months, mean red blood corpuscular volume (MCV) and serum γ-glutamyl transferase (GGT) activity (Chick et al., 1981), and also serum aspartate aminotransferase (AST) activity and urinary ethanol concentration were all assessed. At the end of the study, the Alcohol-Related Problems Questionnaire (Patience et al., 1997) was administered; this contains eleven questions about problems in relationships with friends or family, or the areas of health, work or the law. Attempts were made to contact patients who did not attend by telephone and letter, in order to obtain missing data.

At completion of the study, each patient was asked to rate how effective his or her ‘control’ in abstaining from alcohol had been during the study. Each investigator was asked to rate in a similar way their patients’ success in ‘control’.

**Compliance.** Returned tablets were counted. Failure to attend or to return the tablet bottle at a subsequent visit, was recorded as ‘no data’. Some patients were permitted to reduce their daily dosage if they suffered unwanted side-effects. This was taken into account when assessing compliance.

<table>
<thead>
<tr>
<th>DATE</th>
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<tbody>
<tr>
<td>Have you had any alcoholic drink today? (Yes or No)</td>
</tr>
<tr>
<td>How was your sleep last night? (see scale below)</td>
</tr>
<tr>
<td>How many units of alcohol have you had today in total? (see scale below)</td>
</tr>
<tr>
<td>How was your appetite today? (see scale below)</td>
</tr>
<tr>
<td>How was your mood today? (see scale below)</td>
</tr>
<tr>
<td>MEDICATION</td>
</tr>
<tr>
<td>How many study tablets have you taken today? (No. of tablets)</td>
</tr>
</tbody>
</table>

Please complete this card every evening until your next visit to the hospital. Please use a black pen.

**Units of Alcohol**

| half pint beer  = 1 unit |
| half pint cider = 1 unit |
| 1 glass of wine  = 1 unit |
| 1 measure of spirits = 1 unit |
| 1 bottle of spirits = 30 units |

**Sleep/Appetite/Mood Scores**

| 0 poor |
| 1 moderate |
| 2 good |
| 3 excellent |

Please put the appropriate number in the box to record your score.

Fig. 2. Monthly daily record card.

**Typology categorization.** A retrospective categorization of the patients enrolled in the Edinburgh and London centres was undertaken using the Lesch typology algorithm, which has been used to predict response to acamprosate (Lesch and Walter, 1996). Patients were traced through contact addresses, hospital and primary care National Health Service Records, and the Register of Deaths. The data necessary to classify a patient were obtained at interview by a psychologist from the Lesch clinical group, supplemented if necessary from clinical records, and the research database. Classification was based on a computer-held algorithm. Analysis was made of outcome in relation to typology.

**Analysis**

**Power.** For the primary efficacy variable of abstinence for 6 months, based on previous reports of an expected placebo response of 25% and an expected response to acamprosate of 40% (Lhuintré et al., 1985), a sample of 512 would have a 95% power of detecting a difference between treated and untreated patients using a 5% significance level and a two-tailed test.

**Efficacy.** Following the intention to treat (ITT) principle, any randomized patient who took at least one dose of study medication was entered into the analysis. It was assumed that all patients who terminated treatment before the end of the study, including those experiencing adverse events, were treatment failures. Primary efficacy variables were pre-defined as: duration of continuous abstinence; duration of continuous abstinence or controlled drinking. Abstinence was defined as: diary card available and no reported drinking and negative breath and/or urine alcohol levels. Controlled drinking was defined as mean daily self-reported consumption of 5 units or
below (men) or 3 units or below (women) and no single day exceeding 8 units (men) or 6 units (women). A unit was that amount of beverage containing 8 g of ethanol. Secondary outcome variables were cumulative abstinence duration, and craving for alcohol.

Compliant subgroup. A subgroup of more compliant patients was identified post hoc as those who (1) met inclusion criteria; (2) did not take any prohibited medication during the first 14 days on study medication; (3) attended at least one of the scheduled visits in the first 2 weeks after starting medication; (4) took at least 50% of study medication according to tablet counts during the first 14 days. Excluded from this subgroup were 24 patients who had not met the initial inclusion criteria, but which had not been identified at the outset.

To examine predictors of outcome, subgroups were created according to ratings on certain baseline characteristics (e.g. gender) and the proportions of good responders in the two treatment groups were compared either using $\chi^2$ or two-tailed Fisher’s exact probability tests, as appropriate. Multiple regression analysis was used to examine the significance of these relationships.

RESULTS

Recruitment to the study

An unspecified number of patients was considered or approached without formal evaluation of eligibility. Staff were asked later about their reasons for pre-recruitment exclusion; the commonest were medical or psychiatric unfitness, patient’s refusal, or patient requesting disulfiram. A total of 664 patients were formally examined for eligibility to enter the study. Of these, 83 did not go forward to randomization. These 83 comprised: 24 lost to follow-up between assessment and randomization, 40 failed to meet inclusion criteria, three showed worsening of their condition, 10 changed their minds about taking medication or otherwise withdrew co-operation, and in the remaining six no reason for exclusion was specified.

Thus 581 patients were randomized and included in the ITT sample.

Baseline data

At the point of randomization, the acamprosate (A) and placebo (P) groups were well matched on the following variables: age (A 42.8, P 43.8 years), gender (A 87% male, P 80% male), marital status (unmarried: A 43%, P 45%), and employment status (unemployed: A 51%, P 46%); pattern of drinking (‘episodic’: one-third of each group); mean SADQ score (A 34, P 33), CAGE [a score of 4 in 76% (A) and 74% (P)] and MAST [mean score 38(A), 37(P)], including being matched for those items in MAST with an antisocial component (involved in fights, been arrested, trouble with police, drunk driving), blood MCV (A 98.3, P 98.2 fl), serum GGT (A 122 U/l, P 108 U/l, n.s.); mean craving at baseline (A 24 mm, P 22 mm, not significant).

The groups were not matched on: prior weekly alcohol consumption (A 188 units/week, P 168 units/week, $P = 0.022$); place of detoxification (home not hospital: A 55%, P 45%, $P = 0.020$).

The mean interval between the beginning of detoxification and start of study medication was 24 days (A), 25 days (P). However, in 158 patients (27%) (A 74, P 84) this was between 29 and 42 days and in 34 patients (6%) (A 18, P 16) between 43 and 56 days. Patients for whom there was more than 5 weeks between the beginning of detoxification and randomization should not have been included according to the protocol; however, some were randomized and therefore are included in the analysis except when stated. Some patients (168) drank alcohol in the 7-day ‘wash-out’ period between the assessment intake interview and the start of study medication. This was controlled drinking in 13% (A) and 16% (P), and uncontrolled drinking in 15% (A), 14% (P), with no data available in 3% of patients in each group.

Attendance

There were no statistically significant differences in attendance between the treatment groups at any time point in the study. At the mid-point of the study (84 days) 51% of the acamprosate group and 54% of the placebo group attended; this fell to 35% (A) and 37% (P) by the 24th week. Only 203 patients completed the study [A: 100 (35%), P: 103 (35%)]. The commonest reasons for early withdrawal were: lost to follow-up (A 23%, P 25%), adverse events (A 14%, P 9%), condition worsened (A 7%, P 9%), refused medication (A 11%, P 8%), and ‘non-compliance’ (i.e. missing many appointments) (A 6%, P 9%). A major effort to contact all patients was made 1 month after the end of the medication phase; 486 were interviewed. A summary of patient retention in the study is shown Fig. 3.
Efficacy

Continuous abstinence: survival analysis. The survival curve for complete abstinence is shown in Fig. 4. At randomization to study medication, 32% of patients had already relapsed. No significant differences emerged at any visit in the proportion of patients abstinent, nor in the proportion drinking in a controlled way, between study groups. Continuous abstinence for the 24 weeks was achieved by 12% (A) and 11% (P). A further 3% (A) and 6% (P) drank some alcohol but without meeting criteria for our definition of ‘uncontrolled’.

Cumulative abstinence duration (CAD). CAD is the totalled number of abstinent days recorded on all diary cards for the period between first study medication and end of medication. CAD did not differ between treatment groups: 77 days (A) and 81 days (P) ($P = 0.492$).

‘Control’ and craving. Of the 203 patients still in contact at the end of the study, who answered the question ‘how effective they perceived their ‘control’ in abstaining from alcohol during the study’, 70% (A) and 73% (P) stated ‘good’ or ‘excellent’. In this group of compliant patients, investigators were also positive about the patient’s response to treatment, rating 84% (A) and 82% (P) as ‘success’.

The mean decrease in craving was significantly greater in the acamprosate group after 2 weeks of treatment ($P < 0.001$) and after 4 weeks ($P < 0.001$) and there was a trend at 1 week ($P = 0.079$) and 12 weeks ($P = 0.069$). One month after the end of the medication phase, the mean decrease in craving was greater in the acamprosate-treated patients than in those receiving placebo ($P = 0.022; n = 486$) (Fig. 5).

The scores on the Alcohol-Related Problems Questionnaire medication phase improved during the medication phase between intake and 6 months by the same amount, a mean of 3.8 points, in both groups.

Blood tests

Laboratory test results improved throughout the study in both treatment groups; no significant differences were observed between treatment groups in either mean values at any of the time points or in the percentage change in values from baseline. The proportion of patients attending at each visit with an elevated serum GGT (>50 U/l) did not differ between treatment groups. At visit 1, 50% of patients had elevated serum GGT activities and at the end of the medication phase 29% had raised activities. The proportions of patients having an increased blood MCV (>97 fl) at baseline were 56% (A) and 49% (P). There was no difference between the groups at any visit. At visit 10, increased blood MCV was detected in 35% (A) and 36% (P). For patients completing the study in whom complete data on blood tests were available, the mean GGT corroborated self-reported drinking as recorded in the diary cards (Fig. 6).

Secondary effects

Hamilton Anxiety and Depression scores. At baseline, the means and SD for the Hamilton Anxiety scores were: mean 9.8 ± 8.1 (A) and 9.6 ± 7.9 (P). The mean decrease after 4 weeks was greater in the acamprosate group (2.6 ± 7.7) than in the placebo group (1.0 ± 5.4) ($P = 0.017$). A trend in the same direction was still visible at 3 months ($P = 0.076$), but was no longer apparent at the end of treatment. A significant
difference was, however, again noted at 1 month post treatment ($P = 0.014$). Improvements in the Hamilton Depression ratings were noted overall, without differences between the treatment groups.

**Safety and tolerability**

The most frequently reported adverse events were headache, diarrhoea, nausea and vomiting. The protocol permitted a reduction in the total daily dose from 6 to 4 tablets/day if gastrointestinal symptoms were distressing and this was done in 11.4% of the acamprosate group and 9.2% of the placebo group. Serious adverse events were reported in 83 patients (29%) in the placebo group and 93 (28%) in the acamprosate group. Hospital admission occurred for detoxification in 290 patients (16.9%) in the placebo group and 291 (14.8%) in the acamprosate group. There was no significant difference in outcome in relation to gender: 21.8% of the 96 women attained 6 months of complete abstinence or controlled drinking, compared to 14.6% of the 485 men. Being abstinent in the ‘wash-out’ week before starting study medication, not unexpectedly, predicted, indeed was a necessary condition for, abstinence during the whole treatment period. No patient who drank in the wash-out week attained complete abstinence. However, three patients (one A, two P) who drank in the wash-out week succeeded in not losing control of drinking during the 6-month treatment period. 

**Compliance**

By the end of the first 2 weeks of receiving medication, 57% of patients in each group were taking at least 90% of their tablets. This gradually reduced until the end of the 6-month medication phase, when 27% (A) and 28% (P) met this criterion. A separate analysis of those patients attending and compliant with medication was not conducted. It would have been a small subset and a separate analysis could not be justified.

**SUB-GROUP ANALYSES**

**Sub-groups according to certain baseline characteristics**

The groups were not matched at baseline with respect to where they were detoxified (Table 1). However, this did not have an influence on outcome of the 290 patients detoxified in hospital, 16.9% achieved 6 months of abstinence or controlled drinking, compared to 14.8% of the 291 patients detoxified at home. There was no significant difference in outcome in relation to gender: 21.8% of the 96 women attained 6 months of complete abstinence or controlled drinking, compared to 14.6% of the 485 men. Being abstinent in the ‘wash-out’ week before starting study medication, not unexpectedly, predicted, indeed was a necessary condition for, abstinence during the whole treatment period. No patient who drank in the wash-out week attained complete abstinence. However, three patients (one A, two P) who drank in the wash-out week succeeded in not losing control of drinking during the 6-month treatment period. There was a non-significant trend for those who had had a longer abstinence period between detoxification and starting the study to remain abstinent throughout the study. This is to be expected: patients able to abstain for a month tend to stay abstinent for longer. Baseline craving predicted outcome, with only five of the 106 patients (4.7%) with high craving (>50 cm on the visual analogue scale) achieving controlled drinking or abstinence for 6 months.

When outcome by treatment group was examined in subgroups defined according to the predictor variables in Table 1 (namely: gender; place where detoxified; drinking pattern in baseline week; severity of baseline craving; interval till start of medication) no interaction with acamprosate emerged. Multiple regression analyses including these five variables did not identify an acamprosate effect. This was the finding when either continuous abstinence, or continuous abstinence/controlled drinking, were used as outcome criteria. Although baseline previous weekly consumption had been higher in the acamprosate group, when added to this multiple regression analysis, an acamprosate treatment effect did not emerge. (The slightly higher baseline consumption in the acamprosate group may have reflected the slightly greater proportion of males.)

**Compliant subgroup**

A sub-group was defined excluding early non-compliance with medication in the first two weeks and those patients
randomized but who had been ineligible on inclusion criteria. This group consisted of 378 patients (A 194, P 184). In terms of their baseline characteristics, these groups were slightly unbalanced in that the patients receiving placebo were more likely to be female (P 22.3%, A 13.4%, \( P = 0.024 \)). They were, however, balanced for place of detoxification as well as on all other baseline characteristics. Within this subgroup, there were no differences between those receiving acamprosate and those receiving placebo on any of the outcome criteria, except for craving at weeks 2 and 4 which was lower in the acamprosate group (\( P = 0.045 \) and 0.050 respectively).

There were no significant interactions between treatment group and any of the baseline factors singled out as likely predictors of outcome (gender, previous weekly consumption, place where detoxified, interval to starting medication, drinking between enrolment and commencing medication, and baseline craving). In the 78 patients who started study medication within 14 days of the start of detoxification, four (5%) sustained abstinence, and all were in the acamprosate group (\( P = 0.052 \)).

**Post-medication assessment**

At a minimum of 1 month after stopping medication, 385 patients were assessed. Of these, 203 had completed the study (A 100; P 103) and they tended to be seen at or near to the 1-month point post-treatment; others had withdrawn early for various reasons and hence tended to be seen at a relatively later point than the completers. The proportion of patients abstinent 1 month after medication ended was slightly higher than at the last visit on medication. This was because some patients who had relapsed and terminated before the end of the study were now abstinent. There was no evidence of sudden relapse in drinking when the medication was discontinued.

### Centre differences and psychosocial treatments offered

Analysis of outcomes by centre did not suggest that acamprosate was more effective in some centres than others, but the numbers analysed were small, and the data by centre are not presented here.

Data were available on the psychosocial treatments offered at the 16 centres which contributed most patients to the study. Nine were specialized alcohol problem clinics, five were addiction centres, one was a general psychiatric setting and one a general medical setting which contributed 72 patients. Day-patient facilities were available in 11 centres. All but two centres reported that a typical in-patient stay, if indicated, would be less than 4 weeks, with two centres specifying less than 2 weeks. Cognitive–behavioural group therapy was offered at 13 centres, and out-patient support groups at nine centres. Eight offered ‘educational groups’. Only five offered marital therapy, and five social skills training. Only two centres had on-site meetings of Alcoholics Anonymous (AA), but 14 centres used AA as a resource. The amount of other treatment taken up by patients in the study period was not documented at the time. However, later estimates revealed that, at seven centres, less than 20% of the patients attended appointments outside the research visits, whereas at five centres more than 75% did so. When asked to compare their clinical impression of patients they had recruited to the study, nine centres said that patients recruited had been ‘typical’, but six said they had been ‘less severe’ than typical patients.

### Typology

An attempt was made to trace all 149 patients randomized into the study at the two main centres. Two patients were too cognitively disabled to give an interview, 10 refused, 29 were untraceable and 32 had died. An interview was obtained and a classification made in 76. The two Lesch types tending to be responsive to acamprosate in the Austrian study of Lesch and
Walter (1996). Types I and II, accounted for 25% and 18% of the sample interviewed respectively. Types III and IV, which in the Austrian study tended to be non-responsive to acamprosate, accounted for 15% and 42%. ‘Types’ were equally distributed between the two treatment groups; 17 Type I and II patients received the placebo while 16 received acamprosate. There was no trend suggesting that these Type I and II patients had a better outcome in one treatment group rather than another.

**DISCUSSION**

In terms of abstinence for the duration of study, the success of this patient population was low, at ~11%. Analysing data on the whole population, no evidence of an effect of acamprosate on drinking in the 6 months following detoxification was found. This is not explained by effects of those baseline characteristics which were imbalanced between the groups, namely gender, place of detoxification and mean previous weekly alcohol consumption.

The craving rating at weeks 2, 4 and at the month after medication ceased was lower in patients treated with the active drug.

The findings of this study differ from those of previously published randomized controlled trials (Table 2), all of which have shown that acamprosate improves self-reported abstinence rates in recently abstinent alcoholics, over periods varying from 3 to 12 months of medication, with two exceptions: Roussaux et al. (1996), and Lhuintre et al. (1990) who did not report consumption data. Not all studies reported corroborative advantages in objective markers of alcohol consumption, such as serum GGT activity. There are a number of possible explanations for these contrasting findings.

**Patient characteristics**

Severity of condition or resistance to treatment may have been greater in the UK patient population, than in some other samples. Thus, in the study of Paille et al. (1995), half of the patients treated were receiving treatment for their alcohol problem for the first time. While previous treatment experience was not recorded in the UKMAS sample, it is believed that more than 50% had a history of treatment failure. Where details have been published, it appears that patients’ social supports in the positive studies were greater than in UKMAS. Thus, in the study of Sass et al. (1996), 26% were unemployed, and in the study of Paille et al. (1995), 21% were unemployed, compared to 48% in UKMAS. [In the other negative study (Roussaux et al., 1996) 60% were unemployed and only 20% married, resembling the low social support of the UKMAS sample.]

Response to the MAST questionnaire is sometimes used as an index of severity of alcoholism. However, great caution must be used when comparing MAST scores between cultures, and between samples with differing proportions of men and women, because some items depend on the interaction between the drinker and society. For example, 5 MAST points can be scored for attending AA, but the availability of AA varies between countries; similarly, several points can be scored for legal infringements, but the rate of police activity towards drinkers also varies between societies and in relation to gender. However, the UKMAS sample scored a mean of 37, similar to the Ladewig et al. (1993) sample (mean 38), but higher than those of Whitworth et al. (1996) (mean 32) and Poldrug (1997) (mean 27). The other studies did not use MAST.

Within our population, therefore, we proceeded to examine whether groups of different severity, defined on baseline MAST or consumption, had a greater or lesser response to acamprosate. However, no such interaction was found. The UKMAS sample may have contained a higher proportion of patients with personality disorder than the other studies. No specific measure was used in any study, but there are certain MAST items relating to social disorder, police trouble and violence, which, to illustrate this point, we have calculated as a separate index. The mean score on these ‘sociopathic’ items in the UKMAS patients was 6.5 (SD 2.7, max. score 11), but these data are not available for other studies.

As regards typology, the Austrian study (Whitworth et al., 1996) contained 39% of non-responding patient types, Types III and IV (Lesch and Walter 1996). If the two UKMAS centres are representative of patients from other centres, then the UKMAS sample contained a higher proportion (57%) of Type III and IV than at least one of the studies from continental Europe. However, there was no trend in the limited data obtained to suggest that Type I and II patients had relapsed less if receiving acamprosate than if receiving placebo.

**Pattern of drinking**

One-third of our patients drank episodically rather than continuously. Few data on patterns of drinking are given in the other trials of acamprosate. However, in the study of Whitworth et al. (1996), 18% were episodic drinkers and Poldrug (1997) reported that, in his Italian study, 86% of patients drank on 7 days per week. At this juncture, there are insufficient data to state whether an acamprosate response is more likely in continuous than episodic drinkers.

**Diary card**

Using such a card, which the patient had to return in person, may introduce stricter criteria for monitoring alcohol consumption than employed in some of the previously reported studies. Perversely, it could encourage less accurate overall recording of consumption if the assessors did not also use careful questioning and their clinical sense. We have no way of assessing either of these possibilities, though we can state that the objective marker, serum GGT activity, correlated well with our diary card measures and did not reveal any advantage to the acamprosate group.

**Timing of the medication**

The mean interval between the last drink and the start of medication was 25 days and, in some patients who were randomized and given medication, was over the 5 weeks specified in the protocol. The range of intervals in the other studies was shorter (Table 2). The effect of acamprosate in the German and Austrian studies was most prominent in the first 30 days. In the UKMAS study, only 78 (13%) of the patients began study medication within 14 days of the start of detoxification, and of the four patients who achieved complete abstinence all were in the acamprosate group, a difference which, however, failed to reach significance ($P = 0.052$). Altogether, 35% of patients had relapsed before starting medication. In some of the
<table>
<thead>
<tr>
<th>First author, date, country</th>
<th>Patients entered (n)</th>
<th>Last drink to 1st drug</th>
<th>Duration of treatment (months)</th>
<th>Daily dose</th>
<th>Continuous abstinence (%)</th>
<th>CAD (days)</th>
<th>Serum GGT activity</th>
<th>Study completed %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lhuintr et al. (1985)&lt;sup&gt;a,b&lt;/sup&gt; France</td>
<td>85</td>
<td>~6 days</td>
<td>3</td>
<td>25 mg/kg max. 2250 mg</td>
<td>48% A; 28% P</td>
<td>n/r</td>
<td>'abstinent = normal' GGT A: 1.38 × normal; P: 2.02 × normal P &lt; 0.02</td>
<td>85%</td>
</tr>
<tr>
<td>Lhuintr et al. (1990)&lt;sup&gt;a,b&lt;/sup&gt; France</td>
<td>569</td>
<td>5–30 days</td>
<td>3</td>
<td>1332 mg</td>
<td>n/r</td>
<td>n/r</td>
<td></td>
<td>63%</td>
</tr>
<tr>
<td>Pelc et al. (1992) Belgium</td>
<td>102</td>
<td>n/r</td>
<td>6</td>
<td>1998 mg</td>
<td>27% A; 4% P P &lt; 0.05</td>
<td>A &gt; P</td>
<td>P &lt; 0.01</td>
<td>n/r</td>
</tr>
<tr>
<td>Tempesta (2000) Italy</td>
<td>330</td>
<td>&gt;5 days</td>
<td>6</td>
<td>1998 mg</td>
<td>47% A; 31% P P &lt; 0.01</td>
<td>110 A; 89 P</td>
<td>P &lt; 0.05</td>
<td>n/r</td>
</tr>
<tr>
<td>Ladewig et al. (1993)&lt;sup&gt;b&lt;/sup&gt; Switzerland</td>
<td>62</td>
<td>&gt;4 days</td>
<td>6</td>
<td>1998 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>38% A; 17% P n.s.</td>
<td>122 A; 78 P</td>
<td>P = 0.039</td>
<td>n/r</td>
</tr>
<tr>
<td>Paille et al. (1995)&lt;sup&gt;b,d&lt;/sup&gt; France</td>
<td>548</td>
<td>7–28 days</td>
<td>12</td>
<td>1332 mg (low) and 1998 mg (high)</td>
<td>35% A high 28% A low 19% P (P &lt; 0.01 for A high vs P)</td>
<td>223 A high 198 A low 173 P</td>
<td>P = 0.0005</td>
<td>&lt;uln: 52% A high 45% A low (P &lt; 0.05)</td>
</tr>
<tr>
<td>Roussaux et al. (1996) Belgium</td>
<td>127</td>
<td>n/r</td>
<td>3</td>
<td>1332 mg and 1998 mg</td>
<td>29% A n.s. 33% P n.s.</td>
<td>n/r</td>
<td>No differences in means</td>
<td>70%</td>
</tr>
<tr>
<td>Whitworth et al. (1996)&lt;sup&gt;a,b&lt;/sup&gt; Austria</td>
<td>448</td>
<td>&gt;4 days</td>
<td>12</td>
<td>1998 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18% A; 7% P</td>
<td>139 A; 104 P</td>
<td>P = 0.0007</td>
<td>40%</td>
</tr>
<tr>
<td>Sass et al. (1996) Germany</td>
<td>272</td>
<td>14–28 days</td>
<td>12</td>
<td>1998 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>45% A; 25% P P &lt; 0.005</td>
<td>224 A; 162 P</td>
<td>P &lt; 0.001</td>
<td>trend in favour of A 'significantly lower in A than P'</td>
</tr>
<tr>
<td>Pelc et al. (1997) Belgium</td>
<td>188</td>
<td>14 days</td>
<td>3</td>
<td>1332 mg and 1998 mg</td>
<td>51% A; 15% P P &lt; 0.001</td>
<td>57 A high 52 A low 34 P; P = 0.05</td>
<td>31% P 48% A</td>
<td>49%</td>
</tr>
<tr>
<td>Geerlings et al. (1997) The Netherlands</td>
<td>262</td>
<td>5–28 days</td>
<td>6</td>
<td>1998 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>20% A; 10% P P &lt; 0.02</td>
<td>61 A; 43 P</td>
<td>P = 0.026</td>
<td>(data n/r) n/r. CDT improved A &gt; P (P &lt; 0.016) 1.3 uln; 48% A; 21% P P = 0.0017</td>
</tr>
<tr>
<td>Poldrugeo et al. (1997) Italy</td>
<td>246</td>
<td>&gt;4 days</td>
<td>6</td>
<td>1998 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>48% A; 32% P P &lt; 0.05</td>
<td>99 A; 70 P</td>
<td>P = 0.007</td>
<td>&lt;1.3 uln; 48% A; 21% P P = 0.0017</td>
</tr>
<tr>
<td>Besson et al. (1998)&lt;sup&gt;a,e&lt;/sup&gt; Switzerland</td>
<td>110</td>
<td>&gt;4 days</td>
<td>12</td>
<td>1998 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25% A; 9% P n.s.</td>
<td>137 A; 75 P</td>
<td>P = 0.013</td>
<td>P &gt; A till 270 days P ≤ 0.02</td>
</tr>
<tr>
<td>UKMAS</td>
<td>581</td>
<td>0–56 days</td>
<td>6</td>
<td>1998 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12% A; 11% P n.s.</td>
<td>77 A; 81 P</td>
<td>Reduced in both (n.s.)</td>
<td>35%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Other psychotropic drugs permitted for various periods.
<sup>b</sup>Inclusion specified GGT > 2 upper limit of reference range (uln) and/or MCV > 98 fl (Poldrugeo: and/or > 95 fl).
<sup>c</sup>Less than 60 kg body weight, 1332 mg.
<sup>d</sup>Detoxification as out-patient in 20%; half were receiving treatment for the first time.
<sup>e</sup>Some patients also received disulfiram.

CAD, cumulative abstinence days; GGT, γ-glutamyl transferase; MCV, mean red corpuscular volume; CDT, carbohydrate deficient transferrin; n/r, not reported; n.s., not significant.
published studies (e.g. Besson et al., 1998), patients were withdrawn from the study before medication was started if they were drinking on the day of commencement.

If the calcium channel abnormalities or NMDA receptor changes in the recovering alcohol-dependent patient are most marked in the immediate weeks after the last drink, then it may be that, if acamprosate is to be effective, it should be started as soon after detoxification as possible, or even during detoxification.

There was a very early relapse in our UKMAS sample: 155 (27%) drank in the first 7 days after detoxification, that is, the week between evaluation and randomization during which they were on no medication, and no data are available for a further 33 patients, suggesting that these individuals had already been lost to follow-up and were probably drinking. If acamprosate could prevent this early relapse in, say, half of these patients, then the difference in overall total abstinence rates could have been 16%. In retrospect, if patients had been given a placebo preparation during that period they might have been less likely to drink.

**Location of withdrawal treatment**

Approximately 50% of patients entering the UKMAS study were detoxified as outpatients. This contrasts with other studies, in which home detoxification was uncommon. Even in the study of Paille et al. (1995), only 20% had not been hospitalized for detoxification. It is difficult to see why this should influence the efficacy of acamprosate; it may however indicate that UKMAS patients had slightly lower motivation/were not willing to come into hospital; or it may reflect the relatively low intensity of the UKMAS clinic approaches compared to approaches in the centres taking part in some of the other studies; or that, compared to those in the other studies, UKMAS patients tended to be less severely dependent, which was also mentioned by six UKMAS centres.

**Type of psychosocial treatments offered**

Descriptions of the psychosocial treatments offered in the other studies are sparse. However, it should be noted that, in UK centres, relatively few were offering those psychosocial therapies which are perhaps of most proven value, such as 12-step facilitation leading to regular attendance at AA meetings, marital therapy, social skills training (Miller et al., 1995; Project Match, 1997). Attendance at AA was more common in the German study, in that, during the first month, 25% of patients went to at least one meeting and by the end of the 12 months, 14% were still attending. The figures for the present UK study are not exact, but it is believed that there was much less AA attendance.

**Drop-outs**

In all the other studies, even those of 12-month duration, completion rates were better than in UKMAS. This may reflect higher rates of patients with personality disorder or lack of social resources, or reflect that with some exceptions the UK centres tended to offer a less intensive approach.

Loss to follow-up is a major problem when interpreting results of treatment outcome in alcohol-dependent samples when studies extend over many months. All the studies described here, including UKMAS, reported results analysed using ‘the intention to treat’ principle, which classifies patients who drop out as treatment failures, and does not risk sub-group analyses where original matching between the groups may be lost. It takes no account of whether or not those patients remaining in the study actually complied with treatment. Many consider the ‘intention to treat’ analysis to be the only correct approach in analysing treatment outcome. Nevertheless, one other analysis was carried out here, of the sample defined as those who had not violated the protocol in any way and who complied for the first 2 weeks, taking at least 50% of their medication according to tablet count. However, no evidence of a trend towards an effect of acamprosate on outcome was revealed.

**Was the sample too small to show a treatment difference?**

The effect size in the other studies has been at least the 15% allowed for when the power calculations for the UKMAS study were made: at first sight, the UK result seems unlikely to be due to a lack of statistical power. However, the power calculation had assumed that all patients would be abstinent at the start of the treatment period. The fact that 155 patients were no longer abstinent at the start of treatment would have reduced the statistical power of the study.

**By chance, a negative study has occurred**

As the number of controlled studies of apparently successful treatments increases, the proportion of studies which fail to show an effect may also increase. This may be due to variations in the application of the treatment, characteristics of the sample or treatment setting, or perhaps chance. For example, Morris and Beck (1974) reviewed all the randomized controlled studies of tricyclic antidepressant drugs which had been published up to 1 January 1973. Out of 93 studies, tricyclic antidepressants were more effective than placebo in 61 studies, no difference was found in 32 studies, and there were no studies where placebo was more effective than tricyclic drug. Despite the many negative studies, tricyclic antidepressants became accepted as a valuable therapy for depression. It remains to be seen what will be the eventual proportion of positive to negative studies for acamprosate.

**GENERAL CONCLUSIONS AND COMMENTS**

The weight of results of the other studies reported to date lead to the conclusion that acamprosate is a helpful adjunct to conventional outpatient treatment after detoxification, approximately doubling the number of patients achieving continuous abstinence, and increasing by some 30–40% the cumulative total of days abstinent. This UK study does not support these findings. Contributing to an explanation of this negative result may be loss of statistical power due to a higher drop-out rate and relapse into drinking before starting the drug, but also a background of less intensive treatment in general, although the amount and type of preceding and collateral psychosocial and/or pharmacological treatment which best facilitates response to acamprosate has yet to be specified.

From the other studies it is, of course, clear that not all patients respond. The characteristics of responders have yet to be defined. Perhaps the delta (continuous) rather than the gamma (episodic) alcoholic might respond better (Jellinek, 1960), and our UK sample probably had a much higher proportion (33%) of episodic drinkers than other centres,
particularly the wine-drinking centres of Italy, Austria, France and Southern Germany. Lesch and Walter (1996) showed that a more classical, primary type of alcoholic, rather than the alcoholic with other psychiatric or organic disorder or many social problems, is more likely to benefit from acamprosate. Specification of the optimal patient characteristics and optimal accompanying psychosocial treatments is required so that acamprosate can be used to its best advantage.

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REFERENCES


