DOES PSYCHOSOCIAL TREATMENT ENHANCE THE EFFICACY OF ACAMPROSATE IN PATIENTS WITH ALCOHOL PROBLEMS?

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Abstract — Aims: Acamprosate in combination with psychosocial treatment has been shown to be effective for the treatment of alcohol dependence. The goal of the present study was to determine whether the addition of psychosocial intervention to the medical prescription of acamprosate contributes to treatment outcome. Methods: Patients (n = 248) meeting DSM-IV criteria for alcohol dependence or abuse were recruited in 14 outpatient treatment centres and randomized into one of three treatment conditions: acamprosate; acamprosate plus minimal intervention aimed at motivational enhancement (3-weekly sessions of 20 min); and acamprosate plus brief cognitive behavioural therapy (7-weekly sessions of 60 min). Acamprosate was prescribed for 28 weeks, medically monitored by a physician on six occasions lasting 10 min. Drinking behaviour, medication compliance and psychological distress were assessed throughout the treatment period. Follow-up assessment was undertaken 6 months after termination of pharmacological treatment. Results: Of 241 patients with intention to treat (ITT), 114 (47.3%) remained in treatment for the full 28 weeks; 169 of the ITT population (70.1%) were seen for follow-up. No statistically significant differences were found between treatment groups for any of the drinking outcomes either at the end of the 28 weeks of treatment or at 6-month follow-up. There were no statistically significant differences in medication compliance, drop-out rates, or psychological distress. However, a significant interaction effect was observed between treatment centre and treatment group, indicating that brief interventions were differentially effective in different treatment centres. Conclusions: A clear supplemental value of minimal and brief psychosocial interventions to the prescription of acamprosate was not demonstrated. The widely held belief that pharmacotherapy for alcohol dependence should always be combined with psychosocial intervention is debatable and merits further research.

INTRODUCTION

There is an increasing interest in pharmacotherapy for alcohol dependence. In a systematic review of the scientific literature on the efficacy of different agents for the treatment of alcohol dependence, both acamprosate and naltrexone were judged to be quite promising (Garbutt et al., 1999; Swift, 1999). It is generally recommended that such agents be prescribed in combination with some form of psychosocial intervention to provide emotional support, address any psychological or social problems, and increase compliance with the medication (Garbutt et al., 1999). In fact, psychosocial treatment is presently considered an essential component of any treatment programme for substance misuse disorders (American Psychiatric Association, 1995). With recent developments in pharmacotherapy, however, new questions concerning the necessity, nature, and intensity of such psychosocial interventions and the efficacy of particular treatment combinations are arising (Garbutt et al., 1999).

O’Malley et al. (1992) systematically varied the nature of the additional psychotherapy in a randomized, placebo-controlled trial of naltrexone. Naltrexone or a placebo were provided for 12 weeks along with weekly psychotherapy. Patients receiving naltrexone in combination with supportive psychotherapy showed higher abstinence rates than patients receiving naltrexone in combination with coping skills training. If drinking was re-initiated, however, the latter group was found to be less likely to experience a relapse to heavy drinking than the former group. The results of this study indicate that additional psychosocial interventions may be of great relevance for effective pharmacotherapy in alcohol-dependent patients.

In studies of the efficacy of acamprosate, medication was added to the counselling or psychotherapy that was the routine practice of the participating centres. The effectiveness of acamprosate without psychosocial support is unknown, and it is therefore generally recommended that the medication be prescribed in combination with psychosocial support. Studies are nevertheless needed to assess the actual necessity, nature and intensity of the psychosocial intervention.

The purpose of the present study was therefore to examine whether the addition of psychosocial intervention to the medical prescription of acamprosate enhances treatment outcomes. Two psychosocial interventions of known clinical effectiveness (Miller et al., 1995), motivational enhancement and brief cognitive behavioural therapy, were tested. It was hypothesized that the addition of a psychosocial intervention to the medical prescription of acamprosate would significantly reduce treatment drop-out, enhance medication compliance, and both maintain abstinence and prevent relapse. In the light of the broad spectrum of behaviours and issues addressed by cognitive behavioural therapy, it was also expected that such supplemental treatment would significantly reduce psychological distress.

PATIENTS AND METHODS

Study design

A total of 248 patients was randomized into one of three treatment conditions: acamprosate; acamprosate plus minimal...
intervention aimed at motivational enhancement; or acamprosate plus brief cognitive behavioural therapy. A placebo group was not included in the study. Although in clinical practice it is generally recommended to prescribe acamprosate for a period of 1 year, pharmacotherapy was provided for 28 weeks.

Patients were assessed during the selection and inclusion visit (baseline). They were then assessed during weeks 2, 4, 10, 16, 22 and 28 of treatment. Follow-up assessment was undertaken 6 months after termination of the pharmacological treatment.

The patients were recruited from 14 outpatient addiction treatment centres in The Netherlands. Two of the 14 participating centres provided <10 patients, nine of the centres provided 10–25 patients, and three of the centres provided >25 patients. Sealed envelope randomization with balancing by blocks of 15 was used to obtain equal numbers of patients per treatment group from each centre.

All of the patients provided their written informed consent. The trial was performed in compliance with Guidelines for Good Clinical Practice (I. C. H. Expert Working Group, 1996).

Patients

The patients were between the ages of 18 and 65 years. They all met the DSM-IV criteria for alcohol dependence or alcohol abuse (American Psychiatric Association, 1994), had achieved 3–17 days of abstinence, and were clearly motivated to attain long-term abstinence. The criteria for exclusion were renal insufficiency, an antisocial personality disorder, psychotic symptoms, a serious illness unrelated to alcoholism, a history of treatment for epileptic seizures, and current dependence on psychoactive substances other than nicotine and alcohol. Women were required to use a reliable method of birth control and pregnant and lactating women were excluded from the study. Patients were also excluded from participation if they were currently receiving treatment with a non-registered drug, participating in another clinical trial, or had undergone previous treatment with acamprosate.

Treatments

Prescription and monitoring of acamprosate. All patients were prescribed a daily dose of 1332 or 1998 mg (four or six tablets) of acamprosate according to body weight (<60 or >60 kg respectively). The total duration of the pharmacological treatment period was 28 weeks. The patients in each condition were seen by a physician of the addiction treatment centre in weeks 2, 4, 10, 16, 22 and 28 in order to monitor the acamprosate treatment. The appointment was limited to 10 min visits with a focus on the assessment of drinking behaviour and the monitoring of vital signs and other medically relevant aspects of the treatment. Physicians were instructed not to reinforce the patient’s abstinence, not to attempt to increase the patient’s motivation, and not to discuss high-risk situations.

Minimal intervention. This group of patients was monitored as described above and also received minimal intervention consisting of three sessions of 20 min each with the physician in weeks 2, 3 and 4. The overall goal of the intervention was to increase the patient’s motivation using motivational interviewing strategies (Miller and Rollnick, 1991; Miller et al., 1992). In the first session, the costs and benefits of the patient’s drinking behaviour were specified. The physician provided personal feedback about the blood test (γ-glutamyltransferase: γ-GT) and emphasized the need for abstinence. In the second and third sessions, the progress of the patient was discussed together with situations in which the patient was tempted to drink, but succeeded in not doing so. Any lapses were also discussed in a non-judgmental manner and, when necessary, the physician helped renew the patient’s motivation for change by asking what he or she recalled as the most important reason for changing his or her drinking behaviour. The physician also affirmed, complimented, and reinforced the patient in order to enhance self-responsibility and self-esteem. Special attention was paid to medication compliance in every session.

Brief cognitive behavioural therapy. This group of patients was monitored by the physician as described above and also received brief cognitive behavioural therapy from a social worker or psychologist. The cognitive behavioural therapy consisted of five standard and two elective weekly sessions of 60 min each in weeks 2–8. The overall goal of the therapy was to increase the person’s ability to cope with high-risk situations that could precipitate relapse. The therapy was modelled after Monti et al. (1989) and the coping skills therapy manual from Project MATCH (Kadden et al., 1992). During the first 15 min of each session, the drinking behaviour of the patient was reviewed. Medication compliance and motivation for change were enhanced using motivational interviewing strategies. The remainder of the session was devoted to one or more of the topics mentioned below. The patient was asked to bring a partner or ‘significant other’ to the first session. To build the patient’s motivation for change, several components of the Dutch elaboration of Miller’s Drinker’s Check-Up (Miller et al., 1988) were used (Schippers et al., 1994). The patient was also encouraged to monitor good and bad drinking moments. In session two, the therapist provided instructions and trained the patient on problem-solving skills. Cognitive restructuring was addressed in sessions three and four. To meet the individual needs of the patient to the greatest extent possible, the patient and therapist jointly selected two of the eight elective topics as most appropriate. The array of elective sessions was as follows: increasing pleasant activities, managing negative mood and depression, awareness of anger, anger management, assertiveness, drink refusal skills, enhancing social support networks, and couples involvement. The final intervention session was devoted to relapse prevention and supposed to be conducted with all patients.

Treatment integrity

Both psychosocial interventions were manual-guided. The medical prescription and monitoring of the acamprosate was based on a case report form and a number of guidelines. To promote the consistency and quality of treatment delivery, the physicians and therapists participated in a centralized training seminar. All of the contacts with the patients were audio-taped. The adherence of the therapists and physicians to the guidelines for the specific types of intervention and their competence were monitored by reviewing the audio-tapes and supervision by a psychologist.

Coding systems were developed to rate adherence to the treatment manuals during medical consultation, minimal intervention, and brief intervention. Three categories of items were constructed: items essential to the intervention, items...
proscribed in the intervention and items considered compatible with, but not essential to, the intervention (Waltz et al., 1993). A total of 43.3% of the medical consultations, 47.8% of the minimal intervention sessions, and 38.1% of the cognitive behavioural therapy sessions were rated. Overall, the adherence to the manuals and the guidelines was judged good to very good (Disveld, 1997).

Assessment

At baseline, alcohol abuse or dependence was diagnosed using the Composite International Diagnostic Interview for DSM-IV (CIDI 2.1: World Health Organization, 1997). Sociodemographic information and the patient’s medical and alcohol history were obtained. A physical examination and laboratory tests (γ-GT, alanine aminotransferase, aspartate aminotransferase, mean cell volume and creatinine) were performed. The patient completed a questionnaire to assess current psychological distress (SCL-90 or Symptom Checklist-90: Arrindell and Ettema, 1986).

During treatment, the physician, who was not blind to the treatment group, assessed the patient on six occasions: during week 2, week 4, and every 6 weeks thereafter (weeks 10, 16, 22 and 28). The patient was asked to report on drinking behaviour in the period since the previous visit. Conservative definitions were chosen: abstinence was defined as complete abstinence between two visits, and relapse as the use of any amount of alcohol between two visits. In cases of relapse, the number of drinking days and the number of drinks per drinking day were assessed. Data on concomitant medication and attendance at self-help groups or other treatment agencies for alcohol problems were collected. The occurrence of any adverse events was documented. Compliance with the medication was checked by counting the number of tablets returned by the patient. Psychological distress was assessed in weeks 2, 10 and 28. At the end of the treatment period, physical examination and laboratory analyses were repeated.

Six months after termination of the pharmacological treatment, the subjects were invited for a follow-up visit. Drinking behaviour and psychological distress were then assessed.

Statistical analysis

Sample size calculation was based on the two-sided confirmatory test between continuous abstinence proportions in each group. The abstinence rate for the acamprosate-alone group was assumed to be close to 20%; a difference as large as 20% compared with the two other groups (without Bonferroni correction) should be detected under an α of 0.05, with at least 80% power. The primary outcome criteria for drinking behaviour included total number of abstinent days, rates of continuous abstinence, abstinence rate for the last 6 weeks of treatment, time to first relapse, number of drinks per drinking day and laboratory values. The final sample consisted of 241 patients (97.2%) receiving at least one dose of the medication and thus providing at least one key data point after baseline: the intention-to-treat (ITT) sample. Patients who missed a visit or prematurely withdrew from the study were considered non-abstinent for that particular data collection point. In addition, a per protocol analysis (PP) was performed. All of the patients who completed 28 weeks of treatment and attended all of the additional psychosocial treatment sessions were included in the PP sample (n = 97).

Two-tailed testing with the level of significance set at 5% was used throughout the study. Time to the first relapse was evaluated with survival analysis and log-rank test. χ² Tests were used for analysing abstinence rates during the last 6 weeks of treatment. Total number of abstinent days, level of psychological distress and γ-GT were examined using the Kruskal–Wallis test. Number of drinks per drinking day was examined with the Cochran–Mantel–Haenszel test.

In a post hoc analysis, the influence of subjects’ baseline characteristics and the role of differences between centres was investigated by analysing the variance of the residual variability in the main outcome measure using both centre and the interaction between centre and treatment, by applying a general non orthogonal analysis of variance, calculated through a General Linear Model (sum of squares decomposition type III).

RESULTS

Sample characteristics

Of the 241 patients in the ITT sample, 77 (32.0%) were randomized to receive acamprosate alone, 86 (35.7%) to receive acamprosate plus minimal intervention, and 78 (32.3%) to receive acamprosate plus brief cognitive behavioural therapy (Figure 1).

The data in Table 1 show no statistically significant differences between the treatment groups at baseline in sociodemographic variables, family history of alcohol problems, psychological distress or history and patterns of drinking problems.

Drop-out and treatment compliance

Of the 241 patients, 114 (47.3%) remained in treatment for the 28 weeks. A patient was regarded as a drop-out when he or she stopped the pharmacotherapy before week 28. The drop-out rates and reasons for termination are reported in Figure 1. There were no significant differences in the drop-out rates or reasons for termination across the three treatment conditions.

The mean duration of the treatment was 148.2 days (SD 73.5). There were no significant differences between the three treatment groups in treatment duration [χ²(2) = 0.265, P = 0.876].

Patients who remained in treatment took between 89 and 100% of the prescribed medication. There were no statistically significant differences in medication compliance across the treatment conditions.

Patients receiving medication plus minimal intervention attended a mean number of 2.84 of the intervention sessions (out of three 20-min sessions). Patients receiving medication plus brief cognitive behavioural therapy attended a mean number of 5.32 of the sessions (out of seven 60-min sessions).

Drinking outcomes

Total number of abstinent days. The total number of abstinent days (± SD) was 108.5 ± 71.2 for group 1, 119.1 ± 135.5 for group 2, and 108.1 ± 100.0 for group 3. The total number of abstinent days for the total group of patients was 111.2 ± 72.6 (median 107.6), which is 56.7% abstinent days during 28 weeks of treatment (ITT sample). There were again no statistically significant differences between the treatment groups [χ²(2) = 1.501, P = 0.472]. For the PP sample, the mean number of
abstinent days was 173.9 days (median 183.0) or 88.7% abstinent days. Again, there were no statistically significant differences between the treatment groups [$\chi^2(2) = 5.109$, $P = 0.078$].

Rates of continuous abstinence. The ITT results showed that 13.0% of the patients in group 1, 20.9% of group 2, and 10.3% of group 3 were continuously abstinent across the entire 28-week treatment period (Fig. 2). The PP sample yielded the following percentages: 27.0, 40.9 and 18.8% respectively. The differences between the treatment groups for both the ITT and the PP samples were not significant [$\chi^2(2) = 4.006$, $P = 0.135$; $\chi^2(2) = 3.319$, $P = 0.190$ respectively].

Abstinence rates during the last 6 weeks of treatment. As already mentioned, the abstinence rates for the periods between visits were recorded at each visit. An overview of the abstinence rates for the last 6 weeks of treatment is presented in Table 2. Statistical analyses were performed for three categories: abstinent, relapse, and missing. During the last 6 weeks of the 28-week treatment period, 18.2% of the ITT patients in group 1, 24.4% of group 2, and 17.9% of group 3 according to the ITT analysis.
were abstinent; 37.8, 47.7 and 31.3% of the PP sample groups were abstinent. None of the analyses revealed statistically significant differences [χ²(4) = 2.447, P = 0.654; χ²(2) = 1.600, P = 0.449].

**Time to first relapse.** Survival analyses were completed to examine the time to first relapse throughout the 28-week treatment period. The mean (± SD) number of days to the first relapse was 53.4 ± 6.5 for group 1, 65.5 ± 7.0 for group 2, and 55.4 ± 6.5 for group 3 (ITT). There were no significant differences between the treatment groups [χ²(2) = 0.843, P = 0.656]. In the PP sample, the mean number of days to the first relapse was 61.2 ± 9.4, 90.9 ± 9.8 and 41.5 ± 10.3, respectively. Analyses again revealed no statistically significant differences between the PP treatment groups [χ²(2) = 4.761, P = 0.093].

**Number of drinks per drinking day.** During the last 6 weeks of treatment, the mean number of drinks per drinking day for those patients who relapsed was 8.0 ± 6.5 for group 1, 6.1 ± 4.1 for group 2, and 5.1 ± 4.1 for group 3. Statistical tests on the differences between week 28 and the start of the treatment did not reveal significant differences between the treatment groups [Cochran–Mantel–Haenszel(2) = 1.971, P = 0.373].

**Laboratory values.** The mean γ-GT level for those patients who completed the entire treatment period was 52.0 ± 60.6 in group 1, 49.1 ± 54.1 in group 2, and 50.2 ± 88.7 in group 3. The differences between the mean γ-GT level at the start of the treatment and week 28 did not differ significantly between the treatment groups [χ²(2) = 2.520, P = 0.284].

**Psychosocial outcomes.** In week 28 the mean SCL-90 score (± SD) was 131.6 ± 45.1 for the patients in group 1, 119.0 ± 29.7 for group 2, and 132.7 ± 57.3 for group 3. The level of psychological distress had decreased compared with pretreatment levels, but this decrease was similar in the three treatment groups [χ²(2) = 0.884, P = 0.643]. Analysis of the subscales of the SCL-90 questionnaire also revealed no significant differences between the various treatment groups.

Only a few patients attended self-help groups (3.4%) and 22.9% of the patients consulted some other professional for alcohol-related problems during the treatment. In almost every case, it was a general practitioner who was consulted by the patient. There were no significant differences in additional treatments between treatment groups.

**Follow-up after treatment ended.** A total of 169 patients from the ITT population (70.1%) were contacted 6 months after the treatment period ended: 52 from group 1 (67.5%), 64 from group 2 (74.4%), and 53 from group 3 (67.9%) (differences between groups were not significant). With regard to the ITT patients, 13.0, 16.3 and 14.1% of the patients in groups 1, 2 and 3 respectively were found to be continuously abstinent from the end of treatment to follow-up [χ²(4) = 2.547, P = 0.636]. From the start of the treatment to the end of the follow-up period, 9.9% of the patients in group 1, 12.8% of the patients in group 2, and 8.9% of the patients in group 3 were continuously abstinent.

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**Table 1. Baseline sociodemographical and drinking data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acamprosate (n = 77)</th>
<th>Acamprosate + MI (n = 86)</th>
<th>Acamprosate + BCBT (n = 78)</th>
<th>Total no. of patients (n = 241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.3 ± 7.6</td>
<td>44.8 ± 8.7</td>
<td>44.3 ± 9.5</td>
<td>44.5 ± 8.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>65 (84.4)</td>
<td>72 (83.7)</td>
<td>63 (80.8)</td>
<td>200 (83.0)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (15.6)</td>
<td>14 (16.3)</td>
<td>15 (19.2)</td>
<td>41 (17.0)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>74 (96.1)</td>
<td>86 (100)</td>
<td>76 (97.4)</td>
<td>236 (97.9)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3.7)</td>
<td>0 (0)</td>
<td>2 (2.6)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Employment status</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>43 (55.8)</td>
<td>61 (70.9)</td>
<td>36 (46.2)</td>
<td>140 (58.1)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>34 (4.2)</td>
<td>25 (29.1)</td>
<td>42 (53.8)</td>
<td>101 (41.9)</td>
</tr>
<tr>
<td>γ-Glutamyltransferase (UI)</td>
<td>115.8 ± 194.7</td>
<td>92.9 ± 105.1</td>
<td>127.2 ± 246.8</td>
<td>111.1 ± 188.2</td>
</tr>
<tr>
<td>No. of drinks per drinking day</td>
<td>15.7 ± 8.3</td>
<td>14.2 ± 8.2</td>
<td>16.1 ± 9.6</td>
<td>15.3 ± 8.7</td>
</tr>
<tr>
<td>Years of alcohol problems</td>
<td>11.1 ± 7.5</td>
<td>11.8 ± 8.7</td>
<td>12.0 ± 8.2</td>
<td>11.6 ± 8.1</td>
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<tr>
<td>Family member with alcohol problems</td>
<td>43 (55.8)</td>
<td>43 (50.0)</td>
<td>40 (51.3)</td>
<td>126 (52.3)</td>
</tr>
<tr>
<td>Meeting DSM-IV criteria for alcohol dependence</td>
<td>74 (97.4)</td>
<td>84 (97.7)</td>
<td>77 (98.7)</td>
<td>235 (97.9)</td>
</tr>
<tr>
<td>Previous treatment for alcohol problems</td>
<td>46 (59.7)</td>
<td>57 (66.3)</td>
<td>47 (60.3)</td>
<td>150 (62.2)</td>
</tr>
<tr>
<td>Frequency of drinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>50 (64.9)</td>
<td>58 (67.4)</td>
<td>54 (69.2)</td>
<td>162 (67.2)</td>
</tr>
<tr>
<td>Weekends</td>
<td>3 (3.9)</td>
<td>1 (1.2)</td>
<td>6.6 (7.7)</td>
<td>10 (4.1)</td>
</tr>
<tr>
<td>Continuous (not daily)</td>
<td>13 (16.9)</td>
<td>16 (18.6)</td>
<td>11 (14.1)</td>
<td>40 (16.6)</td>
</tr>
<tr>
<td>Episodic</td>
<td>11 (14.3)</td>
<td>11 (12.8)</td>
<td>7 (9.0)</td>
<td>29 (12.0)</td>
</tr>
</tbody>
</table>

Values are means ± SD or numbers (%).

*None of the variables differed significantly across the treatment groups.

MI, minimal intervention; BCBT, brief cognitive behavioural therapy.
Significant differences between the treatment groups were not detected.

The mean level of psychological distress at follow-up (± SD) was 135.3 ± 49.7. Tests on the difference between follow-up and the start of treatment reveal no significant difference between the treatment groups [χ²(2) = 1.376, P = 0.503]. Thus, none of the analyses revealed significant differences between the treatment groups at 6 months follow-up.

**DISCUSSION**

The present study is the first to assess the effectiveness of acamprosate in isolation (i.e. without additional psychosocial intervention). Although the general treatment outcome is lower than in a German acamprosate study (Sass *et al.*, 1996), nevertheless the outcomes for the three treatment groups resemble those of patients receiving acamprosate in placebo-control studies with the Dutch population (Geerlings *et al.*, 1997; Ansoms *et al.*, 2000).

Contrary to our hypotheses, adding a psychosocial intervention to the prescription of acamprosate did not enhance drinking outcomes or compliance with the medication. There was also no reduction in drop-out rates or the level of psychological distress. Even in those patients who completed the pharmacotherapy and who were compliant with the psychosocial interventions, no differences in treatment outcome between the treatment groups were found. Although minimal interventions and brief cognitive behavioural therapy have been shown to be effective for the treatment of alcohol problems (Miller *et al.*, 1998), their supplemental value in combination with pharmacotherapy could not be demonstrated.

It could be argued that the additional psychosocial intervention was not sufficient to produce significant differences in treatment outcome. The patients receiving no psychosocial intervention had, like the other groups, consultations with the physicians six times in 28 weeks. The total contact time with the physician was 1 h. The minimal intervention group was seen in addition for three sessions of 20 min duration each, which only represents an extension of 1 h of contact beyond that of the acamprosate-only group. Being involved in a

**Table 2. Numbers (and percentages) of patients who were abstinent, relapsed, or missing during the last 6 weeks of treatment**

<table>
<thead>
<tr>
<th>Category</th>
<th>Acamprosate (n = 77)</th>
<th>Acamprosate + MI (n = 86)</th>
<th>Acamprosate + BCBT (n = 78)</th>
<th>Total no. of patients (n = 241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinent</td>
<td>14 (18.2)</td>
<td>21 (24.4)</td>
<td>14 (17.9)</td>
<td>49 (20.3)</td>
</tr>
<tr>
<td>Relapsed</td>
<td>23 (29.9)</td>
<td>23 (26.7)</td>
<td>19 (24.4)</td>
<td>65 (27.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>40 (51.9)</td>
<td>42 (48.8)</td>
<td>45 (57.7)</td>
<td>127 (52.7)</td>
</tr>
<tr>
<td>Per protocol sample</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Abstinent</td>
<td>14 (37.8)</td>
<td>21 (47.7)</td>
<td>5 (31.3)</td>
<td>40 (41.2)</td>
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<td>Relapsed</td>
<td>23 (62.2)</td>
<td>23 (52.3)</td>
<td>11 (68.8)</td>
<td>57 (58.8)</td>
</tr>
</tbody>
</table>

*aIntention-to-treat sample: P = 0.654.
*bPer protocol sample: P = 0.449.

For abbreviations, see Table 1.
Table 3. Analysis of variance in the rank-ordered total number of abstinent days (assessed by general linear model, sum of squares decomposition of type III)

<table>
<thead>
<tr>
<th></th>
<th>d.f.</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
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<td>21159.064</td>
<td>21159.064</td>
<td>5.151</td>
<td>0.809</td>
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<tr>
<td>Centre</td>
<td>13</td>
<td>51403.582</td>
<td>3954.122</td>
<td>0.963</td>
<td>0.649</td>
</tr>
<tr>
<td>Treatment</td>
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<td>26072.481</td>
<td>13036.241</td>
<td>1.973</td>
<td>0.183</td>
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<td>Centre.trt</td>
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<td>210741.066</td>
<td>8105.426</td>
<td>1.973</td>
<td>0.183</td>
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<tr>
<td>Dsmtot</td>
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<td>18335.892</td>
<td>18335.892</td>
<td>4.464</td>
<td>0.039</td>
</tr>
<tr>
<td>Age</td>
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<td>48765.432</td>
<td>48765.432</td>
<td>11.872</td>
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<td>195</td>
<td>800952.677</td>
<td>4107.450</td>
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</table>

d.f., degrees of freedom; SS, sum of squares; MS, mean square; centre.trt, centre x treatment interaction; Dsmtot, number of positive answers on the DSM-IV criteria for alcohol dependence.

research intervention itself might also have had a benefit for the patients. While the minimal intervention was relatively limited in time and frequency, the difference between acamprosate medication alone and acamprosate plus brief cognitive behavioural therapy was quite marked. Total contact time offered was extended by a further 7 h, and a broad spectrum of behaviours and issues was addressed. Interventions aimed at teaching coping skills are strongly supported in reviews of alcohol treatment outcome studies (Miller et al., 1998).

In clinical practice, it is generally recommended to prescribe acamprosate for a period of 1 year. However, we believe that prescription of acamprosate for 1 year would not have given different results. Fewer than 50% of the patients completed 28 weeks of pharmacological treatment. In addition, an extended treatment duration would have made the supplemental value of psychosocial treatment even less marked in relative terms. This suggests that yet another explanation for the lack of any supplemental treatment effect must be sought.

A potential explanation of the present findings may lie in biased sample selection. Although the demographic and alcohol-related baseline characteristics of the subjects in this study closely resemble those of the population of patients with alcohol problems seen in the outpatient addiction centres in The Netherlands, it is possible that another bias may have entered: patients with a clear interest in psychosocial treatment might have refused to participate in the study for fear of not being referred to a therapist. This may have influenced the outcomes of the psychosocial interventions in a negative manner.

The integrity and consistency of the different treatments undertaken in the present study were carefully controlled for. The adherence of the therapists and physicians to the manuals and guidelines was good. Only a few protocol violations occurred. In addition, the patients treated in groups 2 and 3 received, as intended, more psychosocial intervention in total, which means that the independent variable was successfully manipulated and that the lack of significant differences between the treatment groups is not a consequence of poor internal validity. The internal validity was also not jeopardized by patients attending psychosocial treatment outside the interventions provided in the study. Few patients attended self-help groups or consulted other professionals for alcohol problems, and numbers of these were not significantly different between treatment groups.

Since the assessing physicians were not blind to the treatment conditions of the patients, it is possible that they might have been biased in their assessments one way or the other. However, we have no indication as to which way, if at all, they might have been biased.

We believe the study was powerful enough to detect differences in outcome between the treatment groups. Also, the outcome measures for drinking behaviour that we used were shown in previous studies to be sensitive enough to detect differences between treatment groups. However, since we found a significant interaction between centres and treatment conditions, we cannot rule out the possibility that, although the general results show no supplemental value of extra psychosocial intervention, in some centres there was a positive effect of additional psychosocial intervention, while in others there was a negative or no effect of such intervention.

We conclude that the supplemental value of minimal and brief psychosocial interventions to the prescription of acamprosate could not be demonstrated in the current study. It is possible that more intensive psychosocial intervention is needed to improve treatment results. Conversely, one can argue that the medical prescription of acamprosate without additional psychosocial intervention is a realistic and sufficient treatment option for at least a particular group of patients. The general assumption that pharmacological treatment for alcohol dependence should always be accompanied by some form of psychosocial intervention is thus open to debate. Further research is, therefore, needed in order to develop evidence-based guidelines regarding the combination of pharmacotherapy and psychosocial intervention for alcohol problems.

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