A COMPARISON OF TWO INTENSITIES OF PSYCHOSOCIAL INTERVENTION FOR ALCOHOL DEPENDENT PATIENTS TREATED WITH ACAMPROSATE

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Abstract — Aims: To compare two levels of psychosocial intervention in combination with acamprosate medication for the treatment of alcohol dependence. Methods: Patients (n = 70) were prescribed acamprosate and randomized to Minimal Psychosocial Intervention (MPI) or Extended Psychosocial Intervention (EPI). MPI patients met a psychiatrist for 20–30 min sessions on four occasions during a 6 month period. EPI patients were offered 10–15 sessions with a psychiatric nurse in addition to the visits to the psychiatrist. EPI patients were trained to use behavioural and cognitive coping skills to deal with high-risk situations in line with a manual developed for relapse prevention. Patients were assessed four times during the 24-week study by self-report and laboratory tests. Results: Patients on average reported a decline in days with heavy drinking and in cumulative number of drinking days. No significant differences between patients in MPI and EPI were found with respect to heavy drinking, cumulative number of drinking days, number of days to first drink, or biomarkers of alcohol consumption. Higher age and lower level of education were significant predictors of treatment success. Conclusions: Adding more intensive individual treatments appears to add no extra improvement beyond that obtained by prescribing acamprosate and offering an infrequent consultation with a physician.

INTRODUCTION

Alcohol dependence is an addictive disorder with complex social, psychological and biological dimensions. Several psychosocial interventions have demonstrated clinical utility in the treatment of alcohol dependence (Crits-Christoph and Siqueland, 1996). Recent progress in the field of alcohol dependence treatment research has also emphasized the neurobiological components of the disease (Garbutt et al., 1999).

A better understanding of the biological mechanisms involved in alcohol dependence has led to the development of acamprosate, a specific drug for the treatment of this condition. Acamprosate (calcium acetylhomotaurinate) acts within the central nervous system, directly towards the basic molecular mechanisms involved in the pathophysiology of alcohol dependence. It is believed to restore the imbalanced GABA-ergic activity induced by chronic alcohol drinking, and inhibit the counterbalancing system involving glutamate (Rammes et al., 2001).

The results obtained from the clinical trials of acamprosate in almost 4000 patients in double-blind, randomized, placebo controlled clinical trials have demonstrated the efficacy of acamprosate in maintaining abstinence in alcohol dependent patients (see, for example, Ladewig et al., 1994; Paille et al., 1995; Sass et al., 1996; Whittworth et al., 1996; Geerlings et al., 1997; Pelc et al., 1997; Poldrugo et al., 1997; Besson et al., 1998; Tempesta et al., 2000; Pelc and Lehert, 2002; Pelc et al., 2002). The combined analysis of acamprosate trials suggests an increase of ~50 to 100% in abstinence rate in patients treated with acamprosate as compared to placebo (Sass et al., 1995; Kranzler and van Kirk, 2001). In meta-analytic studies, acamprosate has also been shown to reduce heavy drinking days (Chick et al., 2003).

O’Malley et al. (1996) suggested that psychosocial and pharmacological treatments are complementary and should be combined to improve treatment outcome. Data from several clinical trials suggest that the addition of acamprosate to diverse psychosocial interventions enhances adherence to such programmes (see, for example, Ladewig et al., 1994; Paille et al., 1995; Sass et al., 1996; Whittworth et al., 1996; Geerlings et al., 1997; Pelc et al., 1997; Poldrugo et al., 1997; Besson et al., 1998; Tempesta et al., 2000).

However, it is not yet clear which is the optimal psychosocial intervention for acamprosate-treated patients, or if treatment efficacy varies with the psychosocial intervention used, as seems to be the case for patients treated with naltrexone (see, for example, O’Malley, 1996).

The aim of the present study was to compare two intensities of psychosocial intervention in combination with acamprosate medication, Minimal Psychosocial Intervention (MPI) and Extended Psychosocial Intervention (EPI). MPI was performed according to the guidelines described by the WHO Brief Intervention Study Group (1996). Patients met a psychiatrist on four occasions during a 6 month period, this relative infrequency being intended to duplicate clinical reality for a typical general practitioner. EPI patients were offered 10–15 sessions with a psychiatric nurse during the 26 weeks of treatment in addition to the visits to the psychiatrist.

The primary hypothesis of this study was that EPI would be more effective than MPI in reducing the number of days with heavy drinking. It was also hypothesized that EPI would be more effective than MPI in reducing the cumulative number of drinking days, in addition to increasing the time to first drink.

SUBJECTS AND METHODS

The study was a single-centre, outpatient, open-label randomized controlled trial with two treatment groups,
Patients who visited the clinic from February 2000–December 2001 due to alcohol problems were consecutively screened for participation in the study. Inclusion criteria were: (1) men or women 18–70 years, (2) a diagnosis of alcohol dependence according to DSM-IV criteria, (3) consumed alcohol on a minimum of 15 out of 90 days prior to screening, (4) residence in Stockholm County (i.e. not homeless), (5) willingness to give informed consent, (6) willingness to stay in treatment for 6 months. Exclusion criteria were: (1) any other substance dependence DSM-IV syndrome except for nicotine, (2) previous treatment with acamprosate or naltrexone, (3) renal insufficiency or other major somatic disease, (4) any other Axis I DSM-IV diagnosis than alcohol dependence, (5) participated in another clinical study in the last 30 days, (6) pregnancy or lactating for female patients, (7) signs of alcohol withdrawal.

If a patient accepted to participate, a signed informed consent was obtained. Patients who declined to participate were offered standard treatment at the clinic, an individually adjusted relapse prevention programme. Out of 192 screened, 70 patients were included. The most common reasons for non-inclusion were: (1) not fulfilling inclusion-criterion number 3, (2) abuse of benzodiazepines, and (3) not fulfilling DSM-IV criteria for alcohol dependence.

Procedure
After recruitment, each participant filled out a Time Line Follow Back (TLFB) form (Sobell and Sobell, 1992) regarding alcohol use during the previous 90 days. TLFB was used both for feedback to the patient at each meeting with the doctor/nurse, and also as source for the primary outcome measures.

A week after screening, the patient again met with the psychiatrist. Patients were required to be abstinent from alcohol during that week. If the patient met that criterion, he or she was randomized to either the MPI or EPI treatment arm. Randomization was by computer-derived randomization list, using blocks of eight. The randomization procedure was unknown to all staff involved in the trial. On this occasion, patients filled out questionnaires on the consequences of their drinking behaviour and a TLFB, both repeated at each of the following sessions. Psychiatric symptoms were assessed at weeks 0 and 24 by Symptoms Check List 90 (SCL 90) (Derogatis and Cleary, 1977).

All patients met the psychiatrist on two additional occasions during the trial (at weeks 12 and 24). During all four visits, the psychiatrist gave patients general guidelines and feedback on their current situation, their drinking behaviour, and how to cope with high risk situations. During these visits, blood (for serum liver enzyme assessment) and urine samples were obtained, and adverse events and concomitant medication or other treatments were reported. At week 24, the completion of a form regarding the patient’s participation in the study served as end-point assessment. Only one psychiatrist was involved in the study. Hence, all patients met the same psychiatrist.

Extended psychosocial intervention
Patients in the EPI met a psychiatric nurse for a minimum of 10 and a maximum of 15 sessions during the trial, in addition to the visits to the psychiatrist. The patients were trained to develop and use behavioural and cognitive skills to deal with high risk situations according to the procedure described in the Project Match manual for relapse prevention (Kadden et al., 1992). The patients and the nurse decided the frequency and interval between sessions with the prerequisite that the total number of sessions should be between 10 and 15. At the first visit to the nurse, the patient received a ‘voucher’ on which he or she could count the number of remaining visits. Each visit lasted ~30–40 min.

EPI was provided by two nurses with board licence in psychiatric care. Both had taken a two week course in the use of the manual, and each had more than 20 years of experience in alcohol dependence treatment but had no formal training in psychotherapy.

Treatment compliance
Patients were defined as completers if they visited the psychiatrist on all four occasions (week −1, 0, 12 and 26) and for EPI patients, visited the nurse on a minimum of 10.

Compliance to concomitant medication
At week 0, all patients were offered acamprosate on prescription as a concomitant treatment to reduce the likelihood of relapse, at a daily dose of 1998 mg for 24 weeks (333 mg tablets; three B.I.D.). All 70 patients accepted acamprosate at this time point, and received a prescription covering 12 weeks. All patients who returned to meet with the study psychiatrist at week 12 were given a second prescription of acamprosate for the remaining study period. None of the patients declined the second prescription of acamprosate. All patients were charged the standard patient’s fee and paid for medication. The total cost during the study was approximately 2700 SEK (240 €). Urine samples were obtained at week 12 and 24, and the presence of acamprosate in the urine was measured by negative ion liquid chromatography-mass spectrometry. The limit of detection was 1 mg/l of undiluted urine.

Analysis of data
The primary outcome variable was defined as the number of days with heavy drinking, as measured by patients’ self-reports in the TLFB questionnaire. The analysis of the primary outcome variable concerned the difference in the number of heavy drinking days between the two groups (MPI and EPI). To accomplish this analysis, the percentage of days with heavy drinking (≥60 g pure ethanol for men and ≥48 g for women) before inclusion in the study was calculated for each patient. Then, the percentage of days with heavy drinking after inclusion in the study was calculated. A repeated analysis of variance was performed to test whether there was a difference between the groups (MPI vs. EPI) in heavy drinking over time.

The second primary outcome variable was the difference in the percentage of days with any drinking between the two groups (MPI vs. EPI). The percentage of days with drinking before inclusion in the study and after inclusion was calculated for each patient and a repeated analysis of variance was performed to test whether there was a difference between the groups (MPI vs. EPI).

As a secondary outcome variable, the time to first drink was compared between the two groups by a one-way analysis of variance.
In addition to these completers analyses, an Intention To Treat (ITT) analysis was performed comparing the two groups with respect to a post hoc definition of successful treatment, defined as a patient who completed the whole treatment and reduced his or her alcohol consumption by 50% with respect to either the number of drinking days or number of days with heavy drinking.

An estimate of the power in the study showed that we had an 80% chance of finding differences between the groups of 0.6 standard deviations or more. This indicates a reasonable chance to find medium to strong effects according to Cohen’s definition.

RESULTS

Basic demographic data are presented in Table 1. No significant differences were found between the two groups for any measure, suggesting a successful randomization. Sixty percent (n = 42) of the ITT sample met the definition of a completer.

First, the difference between the two groups in number of days with heavy drinking was calculated. While the general decline in heavy drinking in the whole sample was statistically significant (F2,68 = 49.4; P < 0.001), the difference in heavy drinking between the two groups was not statistically significant (F1,34 = 3.6; P = 0.07) (Table 2).

Table 1. Demographic measures and DSM-IV criteria for alcohol dependence

<table>
<thead>
<tr>
<th>Variable</th>
<th>EPI (n = 34)</th>
<th>MPI (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>27/7</td>
<td>24/12</td>
</tr>
<tr>
<td>Marital status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Married</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>Divorced</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Other</td>
<td>44</td>
<td>50</td>
</tr>
<tr>
<td>Education (no. of years in school)</td>
<td>12.4</td>
<td>12.8</td>
</tr>
<tr>
<td>DSM IV criteria (out of 7)</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Completers (%)</td>
<td>65</td>
<td>56</td>
</tr>
</tbody>
</table>

Table 2. Alcohol drinking patterns over time for EPI and MPI patients. Results are shown for completers (the three columns to the left) and for non-completers (the three columns to the right). Non-completers are patients who did not visit the psychiatrist at week 12 and/or at week 24.

<table>
<thead>
<tr>
<th></th>
<th>EPI (completers; n = 22)</th>
<th>MPI (completers; n = 20)</th>
<th>Total (completers; n = 42)</th>
<th>EPI (including non-completers; n = 22–29)</th>
<th>MPI (including non-completers; n = 20–32)</th>
<th>Total (including non-completers; n = 42–61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to inclusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with heavy drinking (%)</td>
<td>45.6</td>
<td>54.5</td>
<td>50.1</td>
<td>50.9</td>
<td>59.6</td>
<td>55.5</td>
</tr>
<tr>
<td>Days with drinking (%)</td>
<td>56.2</td>
<td>60.0</td>
<td>58.1</td>
<td>61.1</td>
<td>66.3</td>
<td>63.9</td>
</tr>
<tr>
<td>Week 0–12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with heavy drinking (%)</td>
<td>10.6</td>
<td>18.3</td>
<td>14.2</td>
<td>15.8</td>
<td>20.8</td>
<td>18.2</td>
</tr>
<tr>
<td>Days with drinking (%)</td>
<td>21.1</td>
<td>28.3</td>
<td>24.4</td>
<td>28.0</td>
<td>34.1</td>
<td>30.9</td>
</tr>
<tr>
<td>Time to first drink (days)</td>
<td>32.7</td>
<td>25.8</td>
<td>29.3</td>
<td>29.6</td>
<td>26.9</td>
<td>28.2</td>
</tr>
<tr>
<td>Week 13–24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with heavy drinking (%)</td>
<td>20.2</td>
<td>24.6</td>
<td>22.4</td>
<td>22.6</td>
<td>29.4</td>
<td>26.1</td>
</tr>
<tr>
<td>Days with drinking (%)</td>
<td>33.1</td>
<td>31.1</td>
<td>32.1</td>
<td>38.4</td>
<td>38.5</td>
<td>38.4</td>
</tr>
</tbody>
</table>

While the general decline in the number of drinking days in the whole sample was statistically significant (F2,68 = 36.1; P < 0.001), the difference in number of drinking days between the two groups was not statistically significant (F1,34 = 0.7; ns) (Table 2).

Further, it was tested whether EPI was more effective than MPI in prolonging time to first drink. The results showed no statistically significant difference between the two groups (F1,42 = 0.03; ns) in the number of days the patients managed to abstain from alcohol from the day of inclusion in the trial.

Note that in Table 2, data are shown also for non-completers, i.e. patients who did not visit the psychiatrist at week 12 and/or week 24 (n = 19). Just as for completers, there were no differences between the two groups in the number of days with drinking, number of days with heavy drinking, or time to first drink when non-completers were included. (Nine patients did not give complete consumption data for the 90 days before inclusion.)

Next, an ITT analysis was carried out comparing EPI and MPI. As can be seen in Table 3, 26 of the 70 subjects (37%) were successfully treated according to the definition. The difference between the EPI and the MPI groups was not statistically significant with respect to the proportion of successful outcomes.

The results for the psychiatric assessments showed that there was a general decline in symptoms as measured by the global SCL-90 score (GSI) from 0.9 at week 0 to 0.6 at week 24 (t(38) = 2.2; P < 0.05). However, there were no differences between the two groups regarding GSI scores at week 24 (F1,38 = 0.98; ns).

The results for compliance to acamprosate medication can be found in Table 4. There were no statistically significant differences between the two groups (EPI and MPI) in compliance to concomitant medication.

Further corroborating the lack of differences between the two treatments, there were no statistically significant differences between the two treatment groups with regard to serum aspartate aminotransferase, gamma glutamyl transferase or serum carbohydrate deficient transferrin after 24 weeks in treatment. There was a statistically significant difference between the treatment groups in favour of MPI with respect to serum alanine aminotransferase levels (F1,30 = 4.6;
physician’s decision as to which was most appropriate. Neither Pelc et al. (2002) or Soyka et al. (2002), in these open and non-randomized studies, found differences in treatment outcome according to psychosocial intervention.

It may be argued that in the present study, EPI did not sufficiently add to MPI in treatment intensity to make significant differences in treatment outcome. There is no straightforward answer to the question of how many sessions make sufficient difference between treatments to make a difference in outcome. Pelc and Lehert (2002) offered up to 30 follow-up visits with a community nurse plus physician visits in the intensive treatment arm versus about eight physician visits, whereas in our study, MPI patients met with the psychiatrist for ~1.5 h total while the EPI patients met with the nurses for a minimum of 5 h during the study, making a total of ~6.5 treatment hours. The total ‘time-in-treatment session’ was hence more than four times as long for EPI patients compared to MPI patients, but comprised considerably fewer hours than in Pelc and Lehert’s intensive community nursing follow-up study.

In both treatment arms, teaching coping skills was an element for helping a patient to remain abstinent. A possible explanation to the lack of difference between groups may be that the psychiatrist in the study was a trained specialist in the field, which might have contributed to a high degree of effectiveness of the MPI, hence reducing the differences between the treatment arms.

Being part of a study may in itself make a patient more motivated to remain abstinent. The general reduction in drinking over time in both groups could be related to such an effect. Further, certain study activities, like filling out questionnaires about the consequences of one’s drinking behaviour, is a cognitive activity which has been shown to strengthen a patient’s motivation to remain abstinent (Miller et al., 1991). Further, the fact that the patients were charged standard patients and medication fees may also have an impact on motivation.

The statistical power of the study was calculated to detect differences in treatment outcome between the groups in terms of successful outcome. There was a tendency for EPI patients to be more successful in their treatment than MPI patients. It is possible that with a larger sample of patients a significant difference between the two groups might have been detected. On the basis of the power estimation we could rule out medium to larger effects, while it is possible that smaller differences might have gone undetected. However, it is debatable whether differences which cannot be detected in 70 patients are clinically relevant. The fact that the study was carried out in a single centre suggests reduced treatment variability for patients, further strengthening this notion.

To conclude, the present study did not show that EPI was a more effective psychosocial intervention than MPI when used in combination with acamprosate. According to this result, acamprosate medication combined with infrequent follow-up visits may therefore be an alternative to more intensive individual treatments, and thus be more cost-effective. It is proposed that for many patients with alcohol problems, a treatment provider trained in relapse prevention could provide a sufficiently effective psychosocial intervention with only a few sessions. It is proposed that future research should focus on more intensive treatments in order to give further

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Table 3. Distribution of patients in MPI and EPI according to successful outcome of treatment (defined as a 50% reduction in the number of drinking days or a 50% reduction in the number of heavy drinking days as well as completion of the whole study)

<table>
<thead>
<tr>
<th></th>
<th>EPI (n = 34)</th>
<th>MPI (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful treatment</td>
<td>44% (n = 15)</td>
<td>31% (n = 11)</td>
</tr>
<tr>
<td>Unsuccessful treatment</td>
<td>56% (n = 19)</td>
<td>69% (n = 25)</td>
</tr>
</tbody>
</table>

Table 4. Results for compliance to acamprosate for patients in EPI and MPI. The figures show the number of patients who showed positive or negative tests for acamprosate in the urine at week 12 and 24

<table>
<thead>
<tr>
<th></th>
<th>EPI</th>
<th>MPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>Week 12</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Week 24</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

$P < 0.05$ but that difference disappeared after Bonferroni correction to reduce the risk of spurious significances.

The association of two non-treatment factors with outcome was measured. Higher age ($F_{1,67} = 6.1; P < 0.05$) and lower level of education ($F_{1,57} = 7.3; P < 0.01$) were significant predictors of treatment success.

DISCUSSION

The present study did not support the primary hypothesis that EPI would be more effective than MPI when combined with acamprosate in reducing heavy drinking over 6 months. Neither did the result show any differences between the groups in cumulative number of drinking days (CAD), time to first drink (TFD), or in the post hoc ITT analysis according to the definition of successful outcome. This was corroborated by the lack of differences between the groups regarding the biological markers for alcohol consumption and the assessments of psychiatric symptoms.

This is in line with De Wildt et al. (2002) who found no differences in treatment outcome for patients who received different levels of psychosocial intervention in combination with acamprosate. In contrast, Pelc and Lehert (2002) reported a difference in treatment outcome as a function of different levels of psychosocial intervention in combination with acamprosate. They compared two groups of patients who used acamprosate as concomitant medication, where the first group made only evaluation visits at the clinic, while a psychiatric nurse followed the other group for the whole treatment period in addition to the evaluation visits. It was found that patients who received the latter type of psychosocial support showed better treatment results, compared to the patients who received no psychosocial support. In the two above mentioned studies patients were randomized to the different psychosocial intervention groups. Two other recent studies (Pelc et al., 2002; Soyka et al., 2002) addressed a similar question as to whether certain psychosocial interventions add to the efficacy of acamprosate. In these two multi-centre studies, patients were allocated to psychosocial intervention according to the
guidelines on which level of treatment makes a difference compared to MPI.

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REFERENCES


