A PRAGMATIC TRIAL OF ACAMPROSATE IN THE TREATMENT OF ALCOHOL DEPENDENCE IN PRIMARY CARE

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Aims: To assess the effectiveness of pharmacotherapy with acamprosate in alcohol-dependent patients treated in a naturalistic setting in primary care in France. Methods: The ARES (Acamprosate et Répercussions Economiques et Sociales; Acamprosate and Economic and Social Repercussions) study was performed by 149 general practitioners interested in treating alcohol use disorders in France who included patients fulfilling DSM-IV criteria for alcohol dependence. The only exclusion criteria concerned contra-indications to acamprosate, co-medication with naltrexone and multiple substance abuse. Eligible patients were randomized to one of two treatment arms, either standard care alone or standard care with acamprosate, using an open-label design and followed up quarterly for a period of 1 year. The primary outcome variable was the change from baseline on the Alcohol-Related Problems Questionnaire. Secondary efficacy variables were abstinence. Clinical Global Impression, quality of life measured with the SF-36 and incidence of adverse events. An intent-to-treat population was used for outcome analysis. Results: 422 patients were included, of whom 348 (82%) completed the protocol as planned. At the end of the study, patients randomized to the acamprosate group had significantly better outcomes in terms of total ARPQ score, change from baseline (−2.61 vs −3.44) and number of subjects with no alcohol-related problem. On average, patients treated with acamprosate had one less alcohol-related problem than did the controls. The number needed to treat in order to save one additional patient from alcohol-related problems compared to standard care was 7.14. Statistically significant differences in favour of the acamprosate group were observed for all secondary efficacy outcome measures including quality of life. Conclusions: Adjunctive therapy with acamprosate in primary care is associated with significantly better functional outcome. Pragmatic trials in alcohol dependence are both feasible and informative.

INTRODUCTION

Acamprosate is used in conjunction with psychosocial or behavioural counselling to promote abstinence in alcohol-dependent patients following acute detoxification. This drug is believed to act by attenuating the hyperexcitability of the central nervous system caused by chronic exposure to alcohol. Although the precise mechanism of action of acamprosate is unknown, recent studies have implicated a role for an interaction with metabotropic or N-methyl-D-aspartate-type excitatory amino acid receptors or both (Harris et al., 2002, 2003). Acamprosate could thereby attenuate the excitatory effects of glutamic acid, believed to be involved in the hyperexcitability seen in alcohol withdrawal, as well as the potential neurotoxic effects of this neurotransmitter.

Acamprosate has been studied in 16 randomized clinical trials performed in Europe, and demonstrated to have an abstinence-promoting effect in recently detoxified subjects with alcohol dependence, as well as a favourable safety and tolerability profile (Garbutt, 1999; Mason, 2001). A recent meta-analysis of these 16 studies has quantified the relative benefit of remaining continually abstinent 6 months after detoxification in subjects treated with acamprosate. This relative benefit was of 1.47 compared to subjects receiving placebo (Mann et al., 2004). The meta-analysis also suggested that the relative benefit attributable to acamprosate may increase over time.

It is not clear exactly how, however, these data on the clinical efficacy of acamprosate should be transposed to the everyday treatment of alcohol dependence in the community. There are a number of reasons for this. Firstly, the conditions of the randomized clinical trial differ considerably from treatment in the community. The trials are generally conducted in academic centres, as opposed to the general practitioner’s surgery or community alcohol rehabilitation centres, entry criteria of the trials limit the extent to which the patients evaluated are representative, and outcome criteria do not necessarily reflect pragmatic treatment goals. Secondly, participation in clinical trials requires motivation on the part of both the patient and the physician; it is however well established that motivation is in itself an important determinant of a favourable outcome. Finally, the very process of participating in a trial, with its requirements for regular follow-up visits, in-depth patient–physician interview, and rigorous self-monitoring of drinking behaviour may well be a form of psychosocial therapy of alcohol dependence in itself. There have been several Phase IV studies performed with acamprosate in more naturalistic conditions that have gone some way to meeting these objections (e.g. Pelc et al., 2002; Soyka et al., 2002), but the real clinical effectiveness in the routine care of alcohol dependence in the community remains unquantified.

Resource allocation by healthcare providers ought to be based on unambiguous assessments of the costs and benefits of alternative treatment options. These are usually generated from models that extrapolate data from clinical trials to patterns of care in the community. However, if the transposition of the clinical trial results to standard care does not match perfectly, this creates a potential source of bias in
such models. For this reason, it is necessary to develop data sets that accurately reflect typical conditions of routine care and at the same time provide reliable numerical data on the added value of particular treatment options. It is the role of the pragmatic clinical trial in a naturalistic setting to generate such data on clinical effectiveness (McRae et al., 1989).

Over the last 10 years, pragmatic trials have come to take a significant place in the medical literature. This can be attributed, at least in part, to a paradigm shift in medicine away from a narrowly defined clinical definition of therapeutic efficacy and safety to definitions based on the functional, social and economic impact of different treatment strategies on patients’ lives. In addition, there has been a growing interest among clinical researchers for new methodological approaches inspired by epidemiological methodology, which generate results that can be more easily applied to the everyday activity of physicians.

Like the placebo-controlled trial, the pragmatic trial is a scientific experimental procedure which compares two treatment strategies in quantitative terms. Unlike the explanatory clinical trial, however, the pragmatic trial is performed under naturalistic therapeutic conditions, with a specific methodology aimed at matching patient characteristics, treatment and follow-up to conditions of routine patient care. Chronic diseases, with multiple psychological and social repercussions, are particularly suitable for evaluation in pragmatic trials. Although pragmatic trials in psychiatric disorders have received much attention (Arnaud et al., 1996), alcohol-related pathologies, including alcohol dependence, abuse, excessive alcohol consumption or at-risk drinking, have not yet been studied.

A pragmatic trial of acamprosate in the treatment of alcohol dependence has therefore been performed in order to determine the clinical effectiveness of acamprosate in the treatment of patients with alcohol dependence in primary care.

The objective of the ARES (Acamprosate et Répercussions Économiques et Sociales; Acamprosate and Economic and Social Repercussions) study was to determine the overall impact of abstinence-promoting therapy on patients’ lives, in terms of psychological, social, professional and familial impact, and of quality of life. Apart from the clinical results of this trial, the interest of this study lies in lessons about the specific constraints and pitfalls associated with conducting a pragmatic trial in alcohol-related pathologies and how this information can be used for future trials.

It was decided to conduct the trial in a primary care environment with general practitioners as the study investigators. This choice was made for three reasons. Firstly, the prevalence of alcohol-related problems in general practice is known in France (Huas et al., 1993): in general practitioner consultation, 18.6% of adult patients have alcohol-related problems and 6.3% are alcohol dependent. The results of the study can thus be readily extrapolated to the overall French population, to give an idea of the national impact of treatment. Secondly, the general practitioner is usually the initial medical contact for individuals who have problems with alcohol in France (Parquet and Reynaud, 1999). Finally, it has been demonstrated that treatment retention of the alcohol-dependent patient is better in general medicine than in specialist care (Kiritzé-Topor, 1998; Conférence de consensus, 1999). The problem of patient dropout is a critical issue in alcohol-related pathologies. In randomized controlled clinical trials in alcohol-dependence conducted in academic centres, the proportion of patients lost to follow-up can easily reach 50% over 6 months, even though regular follow-up visits are carefully planned and strict monitoring imposed. On the other hand, the proportion of patients lost to follow-up in general practice can be as low as 16% over 1 year (Huas et al., 1996).

PATIENTS AND METHODS

Participating institutions and study period

Participating investigators were general practitioners (GPs) in France. A random sample of GPs was established from a registry of 25 000 GPs active in France (TVF registry). In order to optimize representativeness, a stratification was imposed respecting the distribution of general practitioners between the different French administrative regions and between communities of different sizes (rural, town, city, etc.). A target of 160 GPs was planned, and these were contacted from the random list using a quota method. During the initial telephone contact, the GPs were screened for the following three criteria: (i) they should be used to managing alcohol-dependent patients in their daily practice and interested in this; (ii) they should have some understanding of clinical trial methodology, and to have participated in at least one randomized clinical trial; (iii) they should be interested in carrying out a pragmatic trial in a naturalistic environment in this patient group. GPs who fulfilled these three criteria were invited to participate in the study.

In fact, 149 general practitioners in France participated in the ARES study. A total of 200 patients per treatment arm were targeted for randomization into the study. Inclusion started in 1998, and the last patient completed the study in 2000.

Patients

Adult patients with a diagnosis of alcohol dependence as defined by the DSM-IV criteria (American Psychiatric Association, 1994) were eligible for the study. In order to maximize representativeness of the patients, minimal inclusion or exclusion criteria were set, each investigator being expected to include any patient consulting for alcohol dependence and orientated towards an acute detoxification followed by a rehabilitation programme. All patients already consulting an investigator and seeking medical help for achieving long-term abstinence from alcohol could be included. A time-window of between 3 days and 2 weeks from the start of acute alcohol detoxification was set for the entry of each patient into the study. The only exclusion criteria related to contra-indications to the prescription of acamprosate (e.g. renal insufficiency, pregnancy, lactation or a history of hypersensitivity to acamprosate) and to potential incapacity to complete the study protocol (patients anticipating unavailability for follow-up during the following year and patients with major psychiatric disorder or dementia). Multiple substance abusers were also excluded from the study, as were patients already taking acamprosate or naltrexone.

Treatment groups

Each eligible patient was allocated to one of two treatment arms, either standard care alone or to standard care with acamprosate. A computer-generated randomization list was
established prior to the study and held in an independent third-party centre. If subjects fulfilled the entry criteria, the investigator contacted the randomization centre for attribution of a subject number specifying the group to which the subject should be randomized. Participating investigators did not have access to the randomization list.

For the purposes of the study, ‘standard care’ was defined as how the participating physician would normally treat alcohol-dependent patients. In France, this generally consists of in- or out-patient detoxification followed by a rehabilitation programme decided by the treating physician. Rehabilitation classically involves some sort of psychosocial therapy (individual psychotherapy, group psychotherapy or occupational therapy), even if this only consists of the general practitioner seeing the patient regularly and discussing progress. In addition, psychosocial support is sometimes complemented by adjunctive drug therapy, with for example, naltrexone, acamprosate or disulfiram. Investigators were permitted to use any of these approaches in the standard care group with the exception of acamprosate and of naltrexone (whose approved indication in France is quite similar, except for treatment duration). Treatment modalities were at the discretion of the investigator, and could be freely adapted to the needs of individual patients.

The acamprosate group received standard care with acamprosate as well. Acamprosate was provided under exactly the same conditions as the physician would normally use for such patients. A dose of 1998 mg/day (six tablets of 333 mg, divided between morning, noon and evening) was prescribed for patients weighing over 60 kg, and, under that weight, a dose of 1332 mg/day was prescribed.

Investigators were asked to encourage participating subjects to take acamprosate regularly and to return all unused medication and empty boxes. The amount of unused medication returned was used to evaluate compliance (raw data not shown in this paper).

The two study groups were treated in parallel, and the treatment period continued for 12 months from the inclusion visit, concluding with a study completion visit. One protocol-imposed visit once every 3 months was requested by the protocol, all other visits being left to the discretion of the participating physician, who would follow up patients as normal. The only concomitant medication that was forbidden was naltrexone.

Outcome measures

The primary efficacy variable was the change from baseline on the Alcohol-Related Problems Questionnaire (ARPQ), a rating scale that measures the incidence of alcohol consumption on patients’ lives with respect to health problems, work problems, financial problems, family and relationship problems and legal/judicial problems (Chick et al., 1991; Patience et al., 1997). The ARPQ consists of eleven questions each with two response modes (absent or present). In the original version of the scale, ‘absent’ responses were scored as 1 and ‘present’ responses as 2; possible scores thus ranged from 11 (response ‘absent’ to all questions, best possible score) to 22 (response ‘present’ to all questions, worst possible score). In the current study, the ‘present’ scores were recoded as 0 and ‘absent’ scores were recoded as 1, so that possible scores ranged from 0 (response ‘present’ to all questions, best possible score) to 11 (response ‘absent’ to all questions, worst possible score), which seemed more logical.

For the purposes of the ARES study, a French version of the ARPQ questionnaire was prepared using a double back-translation methodology similar to that widely used for quality of life scales. The construct validity of the French version of the ARPQ scale was monitored during the course of the ARES study, by comparing the results with outcome measures generally used in randomized clinical trials, in particular the cumulative abstinence duration (Lehert et al., 1997).

Secondary efficacy variables included abstinence, measured as the cumulative abstinence duration proportion (the proportion of the total study duration during which the patient remained abstinent) and the success of treatment from the physician’s point of view measured with the Clinical Global Impression.

Information on drinking behaviour was obtained by questioning of the patient by the investigator. If investigators considered this to be useful, and was part of their standard practice, they could provide the patients with drink diaries to improve the precision of the data received, but this was not imposed systematically by the protocol. Safety evaluation was restricted to adverse event reporting. Data on quality of life were collected at inclusion and at study end using the SF-36 health profile; a patient-completed questionnaire (Ware and Sherborne, 1992).

Biochemical markers of alcohol consumption (transaminases, carbohydrate-deficient transferrin, γ-glutamyltransferase, etc.) were not recorded systematically, although these could be used by the participating investigator to monitor progress and provide feedback to the patient as part of the rehabilitation strategy.

Statistical analysis

All data were controlled, validated and analysed centrally. The population retained for analysis was the full analysis set of the intent-to-treat (ITT) population, defined as all patients randomized into the study.

Missing data were handled using an alternative censoring method, based on an algorithm controlling for all the patient variables documented at inclusion which had been demonstrated to be predictive of successful outcome in alcohol dependence. The censoring method allowed patients leaving the study early for reasons independent of the study variable (e.g. moving house) to be identified, and handled separately to those patients considered as treatment failures. Treatment interruption was considered to be related to alcohol (i.e. relapse), and such patients were considered as non-abstinent, and therefore treatment failures. Given the open nature of the treatment protocol, it was required that any premature study discontinuation be fully documented, on which basis a censoring decision could be taken by a panel of investigators blinded to the treatment group.

The primary outcome variable (ARPP score at study end) was compared between the two treatment arms using Student’s t-test and the Mann–Whitney U-test. Secondary outcome variables were compared using Student’s t-test, the Mann–Whitney U-test, the Mantel–Haenszel test, the χ² test or Fisher’s exact test, as appropriate. A probability level of P < 0.05 was considered to be significant. Analyses were performed using SAS software.
Baseline variables were assessed for a relationship with the outcome variables using, in the first instance, linear regression analysis, followed by a multiple regression analysis incorporating those baseline variables previously identified. The number of patients to be included in the study was determined from \textit{a priori} power calculations, assuming an \( \alpha \)-risk of 0.5, a \( \beta \)-risk of 0.2, a variance of 7.9 and an inter-group difference in ARPQ score of 0.72. These calculations generated a figure of 200 patients per arm that would be required to demonstrate the desired treatment effect.

\textbf{Ethics}

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment), Good Clinical Practices (European Guidelines) and pertinent French legal and regulatory requirements. Written informed consent was obtained from each subject. Patients were free to withdraw from the study at any time for any reason, without effect on their medical care. No patient was offered financial inducement to participate in the study. The protocol was submitted to and approved by the ethics committee of the Centre Hospitalier Universitaire de Nantes, France.

\textbf{RESULTS}

\textit{Patient disposition}

Four hundred and sixty-two subjects were screened for the study in the different participating general practices. This represents on average a little over three patients per practice. Of these, 422 (91.3\%) were entered into the study (Table 1). Those patients who could not be included were essentially those who were already taking acamprosate at the time of screening, in whom acamprosate would be contra-indicated and those who would not be available for the entire study period of 1 year.

Table 2 presents the baseline characteristics of the patients in terms of sociodemographics and drinking history. The average age of the sample was 47.1 years, with a gender ratio of approximately 3:1 (male:female). Fifty percent of the sample were in stable employment and 72\% were living with a partner. Thirty percent of the sample had psychiatric antecedents, and 64\% a family history of alcohol use disorders. The mean age at the onset of alcohol dependence was 22.4 years. The mean ARPQ score at inclusion was 4.2.

Table 1. Patient flow through the study

<table>
<thead>
<tr>
<th>Patients excluded</th>
<th>Standard care</th>
<th>Standard care with acamprosate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Already treated with acamprosate</td>
<td>32 (15.2%)</td>
<td>42 (19.9%)</td>
<td></td>
</tr>
<tr>
<td>Not available for study period</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Health reasons</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature discontinuations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Consent withdrawal</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>13</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

There were no significant differences between the two treatment groups in terms of the 125 baseline variables recorded in the case report form.

Of the 422 patients included, 348 (82.5\%) successfully completed the 1 year follow-up period (Table 1). The principal reasons for premature termination of the study were loss to follow-up and withdrawal of consent. In addition, ten patients died during the study period (none of these deaths were attributable to treatment). No other reason for patient withdrawal was observed in more than five patients. Only two patients withdrew from the study due to the occurrence of an adverse event.

\textit{Primary outcome criterion}

Significant differences were observed between the two treatment groups in terms of total ARPQ score at study end, change from baseline over the study period, and number of subjects with no alcohol-related problem over the study period. All these differences were in favour of acamprosate (Table 3). On average, patients treated with acamprosate had one less alcohol-related problem than did the controls. From the data on the number of problem-free patients, it was possible to calculate the relative risk of having no alcohol-related

Table 2. Patient characteristics at inclusion

<table>
<thead>
<tr>
<th></th>
<th>Standard care</th>
<th>Standard care with acamprosate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>211</td>
<td>211</td>
<td>422</td>
</tr>
<tr>
<td>Age [mean (SD)]</td>
<td>48.2 (11.1)</td>
<td>46.8 (11.4)</td>
<td>47.1 (11.3)</td>
</tr>
<tr>
<td>Gender (M/F; % female)</td>
<td>147/64 (30.3)</td>
<td>161/50 (23.7)</td>
<td>308/114 (27.0)</td>
</tr>
<tr>
<td>Marital status (% married)</td>
<td>61.6</td>
<td>55.5</td>
<td>58.5</td>
</tr>
<tr>
<td>Children at home (%)</td>
<td>43.4</td>
<td>40.4</td>
<td>41.9</td>
</tr>
<tr>
<td>No education (%)</td>
<td>36.0</td>
<td>29.1</td>
<td>32.5</td>
</tr>
<tr>
<td>Out of work (%)</td>
<td>36.0</td>
<td>28.0</td>
<td>32.0</td>
</tr>
<tr>
<td>Monthly income &lt; €1000</td>
<td>40.5</td>
<td>36.2</td>
<td>38.3</td>
</tr>
<tr>
<td>First detoxification (%)</td>
<td>68.3</td>
<td>59.3</td>
<td>63.8</td>
</tr>
<tr>
<td>Psychiatric antecedents (%)</td>
<td>29.9</td>
<td>30.3</td>
<td>30.1</td>
</tr>
<tr>
<td>ARPQ score [mean (SD)]</td>
<td>4.1 (2.2)</td>
<td>4.4 (2.2)</td>
<td>4.2 (2.1)</td>
</tr>
</tbody>
</table>

Table 3. Primary efficacy measure. Alcohol-Related Problem Questionnaire (ARPQ)

<table>
<thead>
<tr>
<th></th>
<th>Standard care</th>
<th>Standard care with acamprosate</th>
<th>( P ) (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>211</td>
<td>211</td>
<td>NS</td>
</tr>
<tr>
<td>ARPQ at inclusion</td>
<td>4.10 (2.16)</td>
<td>4.40 (2.12)</td>
<td>0.004</td>
</tr>
<tr>
<td>ARPQ at study end</td>
<td>1.49 (2.08)</td>
<td>1.09 (1.79)</td>
<td>0.034</td>
</tr>
<tr>
<td>Change in ARPQ</td>
<td>-2.61</td>
<td>-3.34</td>
<td>0.004</td>
</tr>
<tr>
<td>Treatment success</td>
<td>106 (50.2%)</td>
<td>135 (64.0%)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.26 (1.07, 1.50)</td>
<td>1.39 (1.14, 1.70)</td>
<td></td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>1.39 (1.14, 1.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number needed to treat</td>
<td>7.14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) values, except for the treatment successes, which are given as number of patients (%). Treatment successes are defined as those patients with a rating of 0 on the ARPQ across the study. The relative risk, odds ratio and numbers needed to treat are given with their 95\% confidence limits.

*Mantel–Haenszel test.
problems over 1 year between the two treatment groups. For the acamprosate treated patients, this relative risk was 1.26 compared to the placebo group. This corresponds to a number needed to treat of 7.14, i.e. it would be necessary to treat seven patients with acamprosate for 1 year in order to save one additional patient from alcohol-related problems compared to the control group.

Secondary outcome criteria

The cumulative abstinence duration proportion estimates obtained for the two groups were 0.67 (SD = 0.38) for the control group and 0.81 (SD = 0.29) for the acamprosate group, with a statistically significant difference between the two ($P < 0.001$; Mann–Whitney U-test).

On the Clinical Global Impression, 47% of patients in the standard group and 63% of patients in the acamprosate group were considered markedly or moderately improved by the investigator. This difference was statistically significant ($P = 0.001$; $\chi^2$ test).

Quality of life was assessed using the SF-36 health profile measure. At baseline, scores on all dimensions, notably the mental health, role limitation due to mental problems and vitality dimensions were low compared to reference values. No significant differences were observed between the two treatment groups. Over the course of the study, scores rose on all dimensions in both treatment arms (Fig. 1). The SF-36 scores observed at study end in the standard care with acamprosate arm were significantly higher than those observed in the standard care alone group, with the exception of the general health dimension. A difference in scores between the two groups of five or more points (considered a clinically relevant difference) was observed for physical functioning, bodily pain, the two role limitation dimensions, social functioning and health transition. The mean mental health component score rose from 40.4 to 57.4 in the standard care group and from 40.3 to 64.8 in the standard care with acamprosate group. Changes in the mean physical health component score were 52.8 to 64.0 and 52.3 to 69.2, respectively. Inter-group differences in both these summary scores at study end were statistically significant ($P < 0.01$; Mann–Whitney test).

All the baseline variables, as well as compliance with treatment, were assessed individually for their potential influence on outcome, measured with the ARPQ, CAD and SF-36 scores. Those variables that were associated with a better outcome on the ARPQ were no previous detoxifications ($P = 0.014$), presence of alcohol-related health problems ($P = 0.007$) and compliance ($P = 0.001$) (albeit, not a baseline variable). When these variables were evaluated in a stepwise multiple regression analysis, those variables that were significant predictors of outcome were ARPQ score at baseline, compliance and treatment group. Since final ARPQ score was not independent of baseline score, the effect of treatment group was recalculated adjusting for differences in baseline ARPQ score. This generated an incremental improvement in ARPQ score in the acamprosate group compared to the standard care group of 0.51 (95% confidence limits: 0.03; 0.15), compared to an unadjusted incremental benefit of 0.73.

With respect to CAD, baseline variables that individually influenced outcome were familial antecedents of alcohol misuse, revenue, age, employment situation, previous detoxifications, alcohol-related health problems and compliance. In the multivariate analysis, treatment group, familial antecedents of alcohol misuse, age, employment situation, previous detoxifications, alcohol-related health problems and compliance were significant determinants of outcome. When the inter-group treatment effect was corrected for these other determinants of outcome, the added benefit of treatment on the cumulative abstinence duration with acamprosate was found to be +0.15 (compared to +0.13 for the unadjusted data). For the SF-36 scores, determinants of final score were evaluated after adjusting for baseline score. The variables that were most closely associated with a better outcome were treatment group ($P = 0.001$), presence of alcohol-related health problems ($P = 0.013$) and compliance ($P = 0.001$).

DISCUSSION

The principal finding of this first pragmatic trial of acamprosate versus standard care in alcohol dependence was that adjunctive therapy with acamprosate is associated with significantly better outcome as measured with the ARPQ, an outcome measure that relates directly to patients' motivations for treatment. This corresponds to a reduction in the social, medical and economic burden of alcohol dependence for the patient. The proportion of patients reporting no alcohol-related problem during the study period was 50% in the standard care group and 64% in the acamprosate group. This corresponds to a relative risk of having no problems of 1.26, translating into the need to treat seven patients with acamprosate to obtain one additional patient with no alcohol-related problems over 1 year compared to standard care. From the point of view of numbers needed to treat, treatment with acamprosate can be considered as highly beneficial.

Retention in the trial

The proportion of patients completing the study as planned is very high, compared to most placebo-controlled clinical trials in alcohol-dependent patients, where drop-out rates of 50% or more are frequently encountered. This high retention rate may
be due to the undemanding nature of the follow-up visits, to the good relationship between patients and their usual GP or to the lack of constraints on patient activity between visits. Whatever the reason, this result shows that it is possible to maintain alcohol-dependent patients in medically supervised treatment programmes with a high rate of success. The observed dropout rate of 17% is in fact very close to the figure of 16% for the annual dropout rate observed in a previous survey of the outcome of alcohol-dependent patients in primary care in France (Huas et al., 1996). In addition, observed compliance was higher than had been observed in previous placebo-controlled randomized trials with acamprosate. Logistic regression analysis demonstrated a highly significant association between compliance and all the efficacy measures evaluated, although it is not possible to determine in which sense, if any, the causality lies.

**Validity of outcome measures**

In experimental randomized clinical trials with acamprosate, the therapeutic objective was to achieve sustained and complete abstinence. However, this may not always correspond to the patient’s request or to the physician’s approach in community care. Faced with the patient who is clearly having problems with alcohol, the task of the physician is not primarily to stop the patient drinking but rather to help resolve the problems underlying, or caused by, self-destructive drinking behaviour. However, the notion of ‘helping the patient’ is often difficult to translate into a precise therapeutic objective that can be used in clinical practice. Certain experts would defend the notion that definitive absolute abstinence from all alcoholic beverages should be the only therapeutic goal for patients fulfilling diagnostic criteria for alcohol dependence. However, this ambitious, albeit unambiguous, goal is rarely met in everyday practice. Others, on the other hand, would claim that the control of drinking to within the boundaries of ‘normal’ drinking set by the WHO, or even a simple decrease in regular consumption, would be a more reasonable therapeutic objective. Whatever the criterion, outcome measures are difficult to interpret in the context of a pragmatic trial, since the relationship between decreased alcohol consumption and the perceived benefit by the patient or the perceived utility to the patient is unclear.

Since the precise goal in terms of drinking behaviour is difficult to define, and its relationship to problem resolution unclear, it was decided in the current pragmatic study to define the objective not in terms of achieving changes in alcohol consumption, but rather in terms of decreasing problems caused by drinking. This has the advantage of corresponding to the patient’s therapy goal, and at the same time taking into account the different dimensions (medical, psychological, social, etc.) of the impact of alcohol consumption on the patient. For this reason, the ARPQ was chosen as the primary outcome measure. Previous studies with the ARPQ performed in Great Britain have shown the ARPQ global score to be well correlated with the severity of alcohol dependence, as well as with healthcare resource utilization (Patience et al., 1997). The ARPQ also has the advantage of measuring how the patient has been helped by the treatment options proposed by the physician, which is a key feature of pragmatic trials.

In randomized controlled trials, the principal primary outcome measure used has been abstinence or, in some studies, alcohol consumption determined from patient self-report. A problem with using drinking behaviour outcome is that it is determined from the declarations of the patient, with a subsequent risk of inaccuracy due to dissimulation or forgetfulness. Although this is a potential source of error in any study, in the ARES study the reliability of self-reported drinking behaviour may be particularly unsatisfactory since the protocol imposed no structured method to optimize the quality of data capture (such as the use of drink diaries or time-line follow-back interrogation methods). An additional limitation was that regular follow-up visits during the course of the study were not obligatory. The probability of anamnestic error will increase with longer intervals between visits. One advantage of an alcohol-related problem instrument such as the ARPQ over self-reported consumption data is that the items mostly consist of events (e.g. ‘attendance at hospital related to drinking’) and such events, as well as being memorable to the patient may also be available to the general practitioner from other sources than self-report. The use of CAD as a secondary outcome measure allows the results to be compared with those of previous placebo-controlled randomized clinical trials, in which this outcome measure has been used systematically. The cumulative abstinence duration proportion achieved in this study was 0.67 for standard care and 0.81 for acamprosate. In practice, this means that patients taking acamprosate could be expected to remain abstinent for on average 23% longer than patients on standard care, and to experience around 2 months more abstinence during the 1 year treatment period. These CAD values are somewhat better than those obtained in the placebo-controlled clinical trials. For example, in the 1 year randomized trial comparing acamprosate with placebo in France (Paillez et al., 1995), cumulative abstinence duration proportions of 0.61 for acamprosate and 0.47 for placebo were obtained. The superior rates obtained in the naturalistic setting may partly be explained by improved retention in the treatment programme, since dropouts in the clinical trial programme were considered automatically to be non-abstinent.

Quality of life at study end, measured by the SF-36 health profile measure, was also used as a secondary outcome measure. This is a well-adapted and pertinent measure for pragmatic studies and has been used previously in a number of studies of alcohol dependence (e.g. McKenna et al., 1996; Volk et al., 1997; Daepen et al., 1998; Stein et al., 1998), including a large, open-label observational study of acamprosate (NEAT study; Morgan et al., 2004). These have all showed significantly impaired quality of life in alcohol-dependent subjects compared to reference values for the general population, and the low SF-36 scores reported in this study are consistent with this. Indeed, the values reported are close to those observed in the NEAT study for the mental health dimensions and somewhat lower for the physical health dimensions. At study end, quality of life had improved in both treatment groups, although the extent of improvement was significantly greater in the subjects randomized to routine care with acamprosate than in the routine care alone group. Nonetheless, the degree of improvement in the acamprosate group was lower than that observed previously in the NEAT study. As in the latter study, the two role limitation dimensions were those in which the greatest amelioration was noted.
Issues related to a pragmatic study design

The less structured design of pragmatic trials compared to randomized clinical trials creates potential sources of bias that need to be addressed. For example, placebo groups are not used since they do not correspond to any treatment used in standard practice. However, the absence of a placebo group makes it more difficult to prove or disprove that there is no systematic bias in the study. Potential sources of bias include inclusion bias, which we attempted to minimize in the ARES study by the implementation of a centralized randomization procedure to determine the allocation of patients to one or other treatment group. The comparability of the patients in the two arms at baseline in terms of demographic and clinical variables would suggest that the scope for inclusion bias is low. Assessment bias, where the \textit{a priori} opinion of the investigator would affect rating of ‘soft’ end-points, may also arise. We attempted to control for this by the choice of a primary outcome criterion, the ARPQ, whose components were as factual as possible and relatively insensitive to interpretation bias (divorce, problems with the police, hospitalization etc.). Treatment bias (for example, where the investigator would compensate for the absence of an active treatment by using more intense psychotherapy) was more difficult to minimize. Normally, the physician could treat patients with the entire therapeutic armamentarium at the physician’s disposal but it cannot be excluded that individual treatment choices were influenced by whether acamprosate was used. Intensity of follow-up may also have varied between the two treatment groups.

The appropriate study population for pragmatic trials is the ‘intention-to-treat’ (ITT) population, i.e. all patients initially included in the study whether or not they subsequently adhere to the protocol and follow the allocated treatment (Schwartz, 1994). This recommendation is based on a certain coherence between how patients switch treatments in an ITT population of a clinical trial and in primary care. In everyday practice, patients who do not tolerate an initially prescribed treatment will be switched to another. The comparison that best mimics this situation is thus not between Treatment A and Treatment B, but rather between Treatment A initially, then Treatment X, and Treatment B initially, then Treatment X. This is precisely the comparison that is reflected in the ITT population. Changing treatment during the study therefore is not a handicap, but rather reflects real-life strategies that are appropriate to compare. For this reason, the ITT population was retained as the principal population analysed during the ARES study.

Limitations to achieving an adequate pragmatic study design

Although the aim of the ARES study, as indeed of all pragmatic trials, was to reproduce as accurately as possible standard conditions of medical practice in community care, there are a number of features of the study that are not entirely satisfactory in this respect, and these represent important limitations to the study. Perhaps the most significant of these limitations pertains to the participating investigators. Although these were intended to be representative of French GPs in general, they were in fact selected for two criteria. Firstly, participants had to be interested in treating alcohol dependence. Alcohol consumption, even when heavy, is widespread and widely accepted in France, and many general practitioners regard this as a social rather than a medical issue. They are not prepared to use time or resources in recognizing or treating alcohol-related problems, considering that it is up to the patients to alter their behaviour. It was therefore necessary to include in the ARES study only general practitioners who were interested by this pathology, trained, and ready to devote time and resources. The ARES study results are only applicable to a population of physicians with a specialist interest in treating alcohol dependence. Nonetheless, given the question that the ARES study addressed (the effectiveness of acamprosate), this population of GPs is the relevant one, since only those with an interest in treating alcohol dependence would prescribe this drug.

The other selection criteria were that participants were expected to be experienced with clinical trial methodology and willing to participate in the study, which is not the case of all general practitioners in France. This may introduce a bias towards investigators with a more experimental or proactive attitude to treatment. It thus cannot be claimed with certainty that the investigators achieved identical therapeutic results to all French GPs who actually treat alcohol dependence. Moreover, patients treated by this population of participating GPs may not be entirely representative of all alcohol-dependent subjects being treated in a primary care environment in France.

On the other hand, the high level of patient inclusion ensures the representativeness of the patient sample with respect to the general population of alcohol-dependent patients consulting the participating general practitioners for help with alcohol dependence. Moreover, the baseline sociodemographic characteristics of the patients included in the study and their drinking history are typical of alcohol-dependent patients consulting general practitioners in France.

Another potential limitation on the extent to which these findings can be generalized was the imposition of the DSM-IV diagnostic criteria for alcohol dependence in the entry criteria for the study. Although alcohol dependence as defined by DSM-IV is the only approved indication for acamprosate in France, general practitioners do not use these criteria in routine practice. In the ARES study, no quality control was performed on how the diagnosis was made, and there is no information on how the patients included using these criteria differed, if at all, from those that would otherwise have been treated.

CONCLUSIONS

In conclusion, the ARES trial has demonstrated the feasibility of conducting pragmatic trials in the field of alcohol dependence, and the clinical effectiveness of acamprosate in the treatment of this problem under conditions of standard primary care in France.

REFERENCES


