Alcohol & Alcoholism Vol. 40, No. 5, pp. 422–430, 2005 doi:10.1093/alcalc/agh171
Advance Access publication 6 June 2005

A CRITICAL REVIEW OF PHARMACOECONOMIC STUDIES OF ACAMPROSATE

FLAVIO POLDRUGO[1]*, DORIS-ANITA HAEGER[2], SYLVIE COMTE[2], JAN WALBURG[3] and ANDREW J. PALMER[4]

[1]Office for Research and Innovative Projects on Alcohol, Other Addictions and Mental Health, Departments of Psychiatry and Addiction, University of Trieste, Trieste, Italy, [2]Merck Santé, Lyon, France, [3]Jellinek Klinikum, 1001 AS Amsterdam, Netherlands and [4]CORE Center for Outcomes Research, BASEL, Switzerland

(*Received* 31 *January* 2005; *first review notified* 21 *March* 2005; *in revised form* 27 *April* 2005; *accepted* 28 *April* 2005; *advance access publication* 6 *June* 2005)

Abstract — Aims: This review assessed the published data on the cost-effectiveness of acamprosate for the treatment of alcohol dependence. **Methods:** Four Markov modelling studies have assessed the therapeutic benefit and economic impact of acamprosate on the treatment of alcohol dependence. These have evaluated both short-term and long-term outcomes and have used German, Belgian, and Spanish costings. A fifth prospective cohort study collected real outcomes and data on expenditure during a 1 year study follow-up period. **Results:** All five studies have produced consistent results, showing the use of acamprosate, which enhances abstinence rates, to reduce the total costs of treatment and thus be dominant over other rehabilitation strategies not involving pharmacotherapy. In all of the studies, the principal cost-driver is hospitalization. Although there is a short-term increase in treatment costs associated with drug acquisition, these are recovered from long-term savings attributable to reduced hospitalization and rehabilitation costs.

Over the last decade, pharmacoeconomic studies have become widespread in drug development programmes and in health outcomes research. This has been driven by increasing awareness on the part of health care decision makers on the need to contain costs and, in consequence, by the need to ensure that limited health care budgets can be apportioned in such a way that the greatest therapeutic benefit is attained for as many patients as possible. Many innovative treatments represent a clear therapeutic advance over previous treatments, but often at an increased financial cost. Therefore, it is important to ensure that the extra expenditure required to achieve an incremental unit of clinical efficacy is an efficient use of resources compared with alternative interventions.

Alcohol dependence is a common condition associated with high direct and indirect health care costs, principally attributable to the management of secondary comorbidities and lost productivity. Given the prevalence of alcohol-related health problems, the total costs attributable to alcohol use disorders represent a significant proportion of national health care spending. In the US, untreated alcohol-users and drug-users are among the highest cost users of health care (Zook and Moore, 1980). Alcohol-dependent subjects have been reported to consume up to 15 cents for every dollar spent on health care in the US, mostly for the treatment of secondary morbidity (Holder, 1987). A recent study from France has suggested that costs owing to alcoholism correspond to ~1% of the gross national product (Reynaud *et al*., 2001), while in Finland, direct health costs alone represent ~0.6% of the gross domestic product, while the total health costs may reach 4.3% of the gross domestic product (Hein and Salomaa, 1999).

Thus, any treatment programme that interrupts the course of chronic alcohol dependence or reduces its severity may result in significant cost savings for society. Alcohol dependence can be treated to some extent with psychosocial intervention programmes or pharmacotherapy with abstinence-promoting drugs or both. However, in spite of the large amount of information available on the economic costs of alcohol dependence, as well as extensive public awareness of this, there is little data on the cost and savings associated with the different detoxification and rehabilitation strategies used in the management of alcohol dependence. In a 14 year survey of health care spending by 3068 alcohol-dependent subjects identified in a North American health insurance claims database (Holder and Blose, 1991, 1992), total health care expenditure rose with time in a more-or-less linear manner. Costs rose steeply when the alcohol-related problem was identified. From this moment, cost accrual was very different according to whether the individual was successfully treated or not. In untreated patients, costs continued to rise, whereas in treated patients, costs fell to pre-diagnosis values over a 3-year period. Expenditure for 23–55% of the patients fell to below pre-treatment values.

Moreover, little data are available comparing the efficiency of individual psychosocial and pharmacological interventions that have been shown to be useful in treating alcohol dependence. A study by Holder *et al*. (1991) compared the efficiency of 33 different treatment modalities using a semi-quantitative categorical method. This identified large differences between different treatments, with brief interventions being considered the most cost-effective. This analysis was repeated and refined 5 years later (Finney and Monahan, 1996), and the ranking system was somewhat changed. At this time, clinical trials of pharmacological adjuvant therapy for alcohol dependence were available. However, only oral and implanted disulfiram were assessed with the former being considered not particularly cost-effective. As part of Project MATCH, costs and savings were determined in a prospective manner, and compared between different psychosocial interventions (Holder *et al*., 2000). Again, differences in the efficiency of the various treatment options were observed in different patient populations, with motivational enhancement therapy seeming to be the most cost-effective overall.

Currently, the only pharmacological adjuvant therapy for which cost-efficacy studies have been published is

*Author to whom correspondence should be addressed at: Office for Research and Innovative Projects on Alcohol, Other Addictions and Mental Health, Departments of Psychiatry and Addiction, University of Trieste, Via De Pastrovich 5/A, 34126 TRIESTE, Italy. Tel.: +39 40 57 10 77; Fax: +39 40 35 00 10; E-mail: polydrug@units.it

acamprosate. No such quantitative data are available on the cost-efficacy of naltrexone or disulfiram. Acamprosate is an abstinence-promoting drug that has been evaluated widely in clinical trials (Mann, 2004) that have provided generally consistent data on the relative treatment benefit in terms of abstinence rates. A recent meta-analysis of these data has estimated the relative risk of remaining abstinent conferred by a 6 month treatment period with acamprosate in recently detoxified subjects to be 1.47 (Mann *et al*., 2004). In addition, there is evidence that acamprosate can reduce drinking in those subjects who do not remain abstinent (Chick *et al*., 2003).

On the basis of these clinical data, and taking into account the known health care costs associated with alcohol dependence, a number of modelling studies have been performed in order to estimate the efficiency associated with the use of acamprosate in this population. In addition, a further cohort study has measured health care costs and effectiveness directly, comparing subjects taking acamprosate with those without pharmacotherapy. The aim of this review is to provide a critical assessment of these pharmacoeconomic studies in the context of the overall costs of alcohol dependence.

PHARMACOECONOMIC STUDIES OF ACAMPROSATE

To date there have been five pharmacoeconomic analyses of adjuvant acamprosate therapy (Table 1), all of which have compared costs and outcomes between patients treated with acamprosate and patients following an identical rehabilitation regime without acamprosate.

The weaknesses of these studies are that all but one are projections from diverse cost data sources, rather than direct measures of expenditure obtained in actual clinical studies with acamprosate. The majority of these have used Markov models to predict costs and outcomes. The four modelling studies were based on abstinence rates observed in published randomized clinical trials of acamprosate, and known alcohol-related costs. The fifth study was a prospective cohort study performed in Germany, in which real costs were obtained. All studies investigated direct medical costs and two evaluated indirect costs as well. Certain modelling studies evaluated short-term costs only, whereas others assessed long-term projections including estimates of alcohol-related comorbidity and mortality. The various cost variables assessed in the different studies are presented in Table 2.

Markov modelling is a well-established method for following changes in health states over time and assigning economic parameters to outcomes (Briggs and Sculpher, 1998). These models are a form of decision tree analysis where different nodes are arranged sequentially in time using a stochastic approach, with a fixed interval of time between the two nodes, such as 1 year. These nodes correspond to different multinomial alternative outcomes (for example, abstinence or relapse, hospitalization, occurrence of acute hepatitis, etc.). To each of these nodes can be attributed a probability value determining the event which is likely to occur in a given time-period. These probabilities will differ

Table 1. Pharmacoeconomic studies performed with acamprosate

Study	Reference year	Type	Period	Direct/indirect costs	Reference country —clinical	Reference country —costs	Sensitivity analysis
Schädlich and Brecht, 1998	1995	Markov model	Life	Direct only	Germany	Germany	Yes
Portella *et al*., 1998	1996	Markov model	27 years	Both	Pooled[a]	Spain	Yes
Palmer *et al*., 2000	1996	Markov model	Life	Direct only	Germany	Germany	Yes
Annemans *et al*., 2000	1997	Markov model	2 years	Direct only	Austria	Belgium	Yes
Rychlik *et al*., 2001	1997	Prospective cohort study	1 year	Both	Germany	Germany	NA

NA, not applicable.
[a]The clinical reference data for the Spanish cost-benefit study were pooled from a basket of published studies.

Table 2. Cost variables assessed in the different pharmacoeconomic studies performed with acamprosate

Study	Schadlich (Germany)	Portella (Spain)	Palmer (Germany)	Annemans (Belgium)	Rychlik (Germany)
Hospitalization	✓	✓	✓	✓	✓
Rehabilitation costs	✓	✓	✓	✓	✓
Drug acquisition costs	✓	✓	✓	✓	✓
Psychosocial support		✓	✓	✓	✓
Laboratory tests				✓	✓
GP visits		✓		✓	✓
3rd party health costs		✓			
Lost productivity		✓			✓
Travel costs					✓
Judicial costs		✓			

according to the hypothesis being tested (in this case treatment with acamprosate vs no acamprosate) and are estimated either from clinical trial data or natural history databases. At the end of the decision tree are a finite number of health states (e.g. abstinence, death, cirrhosis, and psychiatric disorder) to which an economic cost can be attributed, which takes into account the overall health care resources consumed by the patient all along the trajectory. The distribution of subjects between the finite health states will differ between the two treatments evaluated in the base hypothesis as a function of the probabilities assigned to each node, and thus the final cost is different. Thus, a comparison can be made between the costs and medical consequences accrued following the test treatment and those accrued by a reference group. Hence, the potential clinical benefit attributable to the treatment can be calculated and balanced against the costs of treatment.

The validity of a given Markov model is evidently critically dependent on the accuracy with which the probabilities attributed to each node are known. For this reason, sensitivity analysis is necessary to determine the extent to which the results of the model are affected by varying these input variables. The principal limitations of such modelling techniques are the limited precision of the input probability variables, the arbitrary choice of outcome parameters to include in the model, which may not correspond to real cost drivers in the real world, and the assumption that the different probability values are independent of each other and do not vary with time, which may be difficult to demonstrate. Nevertheless, studies using Markov modelling techniques allow the projection of short-term endpoints (such as abstinence or controlled drinking) to long-term outcomes, such as cirrhosis, hepatic carcinoma, and neurological disease. Such information is often not feasible to obtain in a real prospective study owing to limitations on the duration of the study.

FIRST GERMAN COST-EFFICACY ANALYSIS

The first modelling study to be published evaluated differential costs associated with treatment using acamprosate and placebo in the context of the German health care system (Schädlich and Brecht, 1998). Both groups, active and placebo received standard treatment. Abstinence rates were obtained from a 1 year placebo-controlled clinical trial performed in Germany including 272 subjects, with a 1 year non-treatment follow-up period (Sass *et al*., 1996). The abstinence rates were 39.9% for acamprosate-treated patients and 17.3% for placebo-treated patients. The Markov model simply postulated that the abstinent patients remained healthy (i.e. no additional alcohol-related health care costs), whereas the relapsing patients incurred costs related to further treatment of alcohol dependence and the emergence of specific secondary pathologies (alcohol-related psychosis and alcoholic liver disease). The probabilities of these occurring were determined from retrospective analysis of hospital records. The time-base for the treatment period used in the pharmacoeconomic modelling study exactly matched that used in the clinical trial (2 years). The model predicted that treatment with acamprosate for 1 year would avoid 34 cases of alcoholic psychosis, 226 cases of continued alcohol dependence, 57 cases of acute alcoholic hepatitis, and 28 cases of alcoholic liver cirrhosis for every 1000 subjects treated. The remaining lifetime medical costs associated with these pathologies were identified using standard German health care costs for hospitalization (1993), rehabilitation treatment (1992), and drug acquisition (1995), discounted at 5% per year. All costs were subsequently adjusted for inflation to 1995 values in DM. Costing was performed from the perspective of the German health care system.

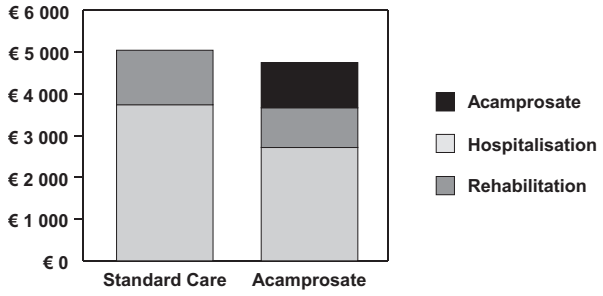

Fig. 1. Cost breakdown for lifetime direct medical costs in patients receiving standard care or standard care with adjuvant acamprosate treatment. Data are taken from the modelling study by Schädlich and Brecht (1998).

This study demonstrated lifetime savings attributable to acamprosate treatment of €1300 (€1450 at 2004 values; lower boundary: €226; upper boundary: €4921) per additional abstinent patient (Fig. 1). These savings were principally owing to reductions in hospitalization and rehabilitation costs. A sensitivity analysis was performed in which values for abstinence rates and duration of hospitalization were varied. Acamprosate use was found to be cost saving in 78% of the scenarios. The principal determinant of efficiency was found to be the differential rate of abstinence. The savings generated also varied according to the unitary hospital costs. The study thus demonstrated that acamprosate use led to a better clinical outcome at reduced cost, and was thus dominant with respect to standard care in terms of cost-efficacy.

A strength of this model is the high degree of confidence with which probabilities could be assigned to the study variables, because these were derived from data from a randomized clinical trial. In addition, the time-frame for the modelling cycle was identical to that used in the clinical trial, allowing the relative abstinence rates of the two treatment groups to be precisely attributed. The clinical source data and the economic costings were obtained within the same time period and the same health care system. Weaknesses of the model are first, the assumption that all abstinent subjects will generate no further alcohol-related health costs (i.e. there are no long-term sequelae of previous drinking in patients who achieve abstinence) may overestimate lifetime savings. Second, the hypothesis that all relapsed subjects will generate identical costs to untreated subjects is likely to be simplistic, although consequences for the results of the model are likely to be minimized by the use of mean costs in the estimates. The most serious limitation is perhaps that the inclusion of only a limited number of study variables in the model, while increasing precision, may have led to the exclusion of important cost drivers.

SECOND GERMAN COST-EFFICACY ANALYSIS

The same efficacy data were used in a second modelling study, also from the German health service perspective (Palmer *et al*., 2000). This predicted long-term clinical benefits and consumption of health care resources accrued in a cohort of males with an average age of 41 years. The principal difference with the preceding study was in the complexity of the Markov model. This started from the same premise of a sustained relatively higher abstinence rate in acamprosate-treated patients, and also assumed that relapsed patients would continue to consume health care resources owing to further treatment of alcohol dependence. However, it was assumed that, at inclusion, excessive lifetime alcohol use would have already led to alcohol-related disease in a significant proportion of patients, resulting in future resource utilization in patients who achieved abstinence. A large number of alcohol-related pathologies were entered into the model, using published epidemiological data to determine the probabilities. These included liver pathologies, gastrointestinal disease, alcoholic psychoses, cardiac myopathy, and peripheral neuropathies. Moreover, the risk of suicide, accidental death, or death resulting from one of the other pathologies were introduced into the model. This enabled the impact of treatment on mortality to be determined, and the cost per life-year gained to be estimated.

This multi-parametric model predicted a lower incidence of acute alcoholic psychosis, hepatic disease, gastrointestinal pathologies, cardiomyopathy, suicide, and accidental death in alcohol-dependent patients treated with acamprosate. This would translate into decreased mortality, with life expectancy in the standard care population being 14.7 years and in the acamprosate cohort being 15.9 years. Discounted at 5% per annum, this corresponded to a life-year gain of 0.52 years attributable to acamprosate.

The lifetime direct medical costs in the acamprosate and standard care groups were calculated using standard 1996 German health care costs for hospitalization, outpatient care, and drug acquisition. In terms of costs, lifetime savings in direct medical costs (discounted at 5% per annum) of €881 (€983 at 2004 values) per patient were predicted in the acamprosate-treated population (Fig. 2). Confidence intervals or other measures of precision were not provided. This figure is rather lower than that put forward by Schädlich and Brecht (see above); this difference could be attributed to the use of a different algorithm and different assumptions in the Markov model, notably the attribution of health costs to the patients who remained abstinent. Nonetheless, this modelling study also demonstrated that the use of acamprosate resulted in significant net lifetime health care cost savings, in spite of the acquisition costs of the drug itself.

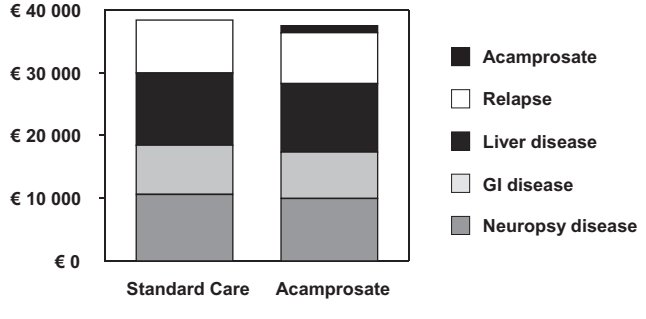

Fig. 2. Cost breakdown for lifetime direct medical costs in patients receiving standard care or standard care with adjuvant acamprosate treatment. Data are taken from the modelling study of Palmer *et al*. (2000), and represent non-discounted costs in 1996 Euro equivalents.

Sensitivity analyses were conducted both for the treatment effect on life expectancy and for the effect on cost. The principal parameters that influenced the results on life expectancy were the probabilities of developing cirrhosis, the suicide rate, and the abstinence rate. Once again, the estimate of abstinence rate was the most important determinant of costs in this model. Nonetheless, even if the long-term abstinence rate in acamprosate-treated patients was assumed to rejoin the abstinence rate of untreated patients after 2 years (the longest duration for which clinical trial data exist), acamprosate was found to be cost-effective. Overall cost savings were indeed predicted in all the scenarios evaluated in the sensitivity analysis, as long as the drug acquisition costs did not rise above €2230 per year (2004 values), which is far higher than its current price.

The principal strength of this model lies in the extensive range of health parameters modelled. In addition, the likelihood that successfully treated subjects would continue to accrue alcohol-related health care costs was taken into account. Economic data and clinical data were obtained from compatible sources. Once again, the weakness of the model is that long-term predictions on costs and medical benefits are made in the absence of any clinical data on the outcome of acamprosate-treated subjects beyond 2 years of treatment. However, the assumption of a sustained benefit is widely accepted and the impact of this assumption was explicitly addressed in the sensitivity analysis that showed acamprosate treatment to be cost-saving even in the absence of a difference in relapse rate beyond 2 years. Moreover, there is no evidence for any rebound effect of acamprosate on drinking following treatment discontinuation.

BELGIAN COST-BENEFIT ANALYSIS

A third study of the direct medical costs of alcohol dependence from a health service perspective in patients treated with acamprosate was performed in Belgium (Annemans *et al*., 2000). This used data from an Austrian placebo-controlled clinical trial of acamprosate (Whitworth *et al*., 1996) to set the abstinence rates in the Markov model for the two treatment groups. These absolute abstinence rates are lower than in the German study, although the treatment effect size is quite similar. Abstinence rates at each time-point from this study were used for each of the monthly stages of the Markov model. Twenty-four 1 month stages were modelled in this study, with treatment with acamprosate being assumed for the first year. The time-frame of the model thus exactly matched that of the source clinical trial.

The Markov model principally evaluated outcomes related to drinking relapse, and the health care costs associated with treating this. These outcomes were outpatient follow-up, institutional follow-up, outpatient detoxification, inpatient

detoxification, loss to follow-up, and death. Each of these outcome states were allocated fixed physician consultation costs, hospitalization costs (acute and long-term), drug costs, and laboratory examination costs. These were based on standard Belgian health care costs in 1997. The only secondary alcoholic comorbidity included in the model was liver disease (cirrhosis, but not liver cancer), as this was the only one the evolution of which was expected to vary as a function of abstinence outcome over the 2 year time-frame of the study. A fixed cost for management of liver disease (€11 977 per year; 2004 values) was allocated to 1% of relapsing patients at each stage of the model, no cost being allocated to abstinent patients.

The direct medical costs per patient over 2 years were calculated to be €5255 (€5796 at 2004 values) for the acamprosate treated cohort, and €5783 (€6379 at 2004 values) for the standard care cohort. The cost savings attributable to acamprosate use were thus €582 per patient over the 2 year period. Once again, the principal cost reductions were those imputable to hospitalization or rehabilitation (Fig. 3). No precision estimates were provided. The authors calculated that extrapolating this data to all alcohol-dependent patients entering detoxification programmes in Belgium could result in overall annual savings to the national health service of €1.74–1.86 million (€1.92–2.05 million at 2004 values).

Sensitivity analyses were performed to evaluate the influence of changes in the assumptions concerning the proportion of patients followed-up for rehabilitation following inpatient detoxification (acamprosate cost-saving at a follow-up rate of $\geqslant$24%), the cost of short-term hospitalization (acamprosate cost-saving at hospitalization costs of $\geqslant$50% of actual costs), and the relapse rate in patients treated with acamprosate (acamprosate cost-saving at a relapse rate of $\leqslant$59%). The latter was thus a critical determinant of cost-efficiency. Again, precision measures for these sensitivity analyses were not provided.

This model presents an advantage over the two previous studies in that it only assessed health care costs over a 2 year period, rather than lifetime. The probabilities assigned to the nodes of the Markov model can thus be estimated with confidence, and no assumptions are made about long-term outcome for which no clinical data are available. On the other hand, the cost data are derived from the Belgian health care system, whereas the clinical data come from an Austrian study in which abstinence rates were somewhat lower than those observed elsewhere.

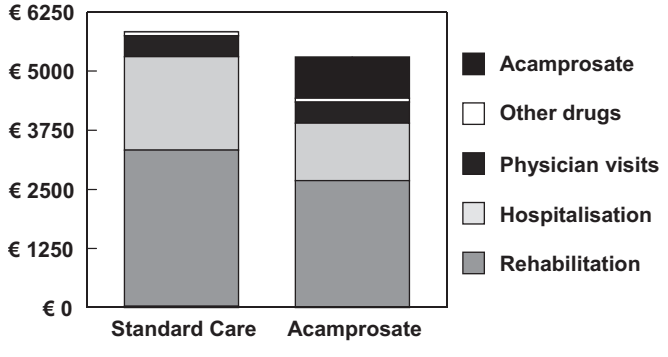

Fig. 3. Cost breakdown for 2 year direct medical costs in patients receiving standard care or standard care with adjuvant acamprosate treatment. Data are taken from the modelling study of Annemans *et al.* (2000).

SPANISH COST-BENEFIT ANALYSIS

A large cost-benefit study performed in Spain (Portella *et al.*, 1998) has a very different scope and methodology from the other modelling studies described above. The study assessed costs attributable to alcohol dependence from both an institutional and a societal perspective, and evaluated an extensive array of direct cost items (hospitalization, physician visits, rehabilitation, and drug acquisition) and indirect cost items (lost working time and productivity, justice system and police costs, and unrelated health expenses). The study used national population reference data to identify an at-risk population for alcohol dependence of 627 400 individuals in Spain and rates of hospitalization for alcohol-attributable illnesses (alcoholic psychosis, alcohol dependence, alcoholic neuropathy, cardiomyopathy, gastritis, and liver disease) to assign outcome probabilities. The time horizons of the study were set by reference to the average age of initiation of treatment for alcohol dependence (42 years), of hospitalization for liver disease (53 years), and of life expectancy in Spain (69 years). Medium-term accrual of indirect costs up to 11 years and delayed accrual of costs attributable to emergent secondary comorbidity from 11–27 years were estimated.

In the first step, the overall lifetime cost of treatment of all alcohol-dependent patients in Spain was determined, using a discount rate of 5% per annum. From this, an annual cost of alcohol dependence of €1657 million (€1975 million at 2004 values) to the Spanish economy was calculated, corresponding to €2640 per patient per year (€3147 at 2004 values). Of the total costs, 25.7% corresponded to direct costs and 74.3% to indirect costs.

In the second step, the lifetime cost saving generated by the successful rehabilitation of an individual patient with no pathological sequelae was estimated to be €23 528 (€28 046 at 2004 values). In the final step, the net cost savings attributable to acamprosate could be determined in each of these scenarios, by incorporating in the model the drug acquisition costs of acamprosate, and a differential abstinence rate calculated from the basket of clinical trials of 29.1% for acamprosate-treated patients and 22.0% for untreated patients. The impact of treatment programmes could then be ascertained in a variety of scenarios, relating to the prevalence of alcohol dependence, the proportion of patients achieving stable abstinence, and the proportion of rehabilitated patients free of post-detoxification comorbidity. Net cost savings were identified for acamprosate treatment regardless of the scenarios envisaged. In the base-case scenario (50% of patients treated, differential abstinence rate of 29.1%, and 50% of patients with no long-term consequences) total potential cost savings were estimated as €210 million (2004 values). These savings carried from €39 million (2004 values) in the most conservative scenario (40% of patients treated, differential abstinence rate of 10%, and 25% of patients with no long-term consequences) to €261 million (2004 values) in the most optimistic scenario (60% of patients treated, differential abstinence rate of 29.1%, and 75% of patients with no long-term consequences).

Again the strength of this model lies in the range of variables and outcomes assessed, and indeed this is the only study to have estimated indirect costs and savings. The clinical data were obtained from a basket of clinical trials performed in different countries, which, on the one hand, more closely approach 'average' treatment outcomes compared with single studies in which observed abstinence rates may be dependent on individual study protocols. On the other hand, the assumptions that these pooled abstinence rates are applicable to treatment programmes for alcohol dependence in Spain cannot be tested. However, a subsequent clinical trial performed in Spain (Gual and Lehert, 2001) provided an estimate of the differential abstinence rate of 35%, somewhat higher than that used in the modelling study. Indeed, inspection of abstinence rates between studies performed in different countries shows the treatment benefit attributable to acamprosate to be quite similar from one study to the other (Mann, 2004). The relative benefit in terms of continuous abstinence associated with 6 months of treatment with acamprosate estimated in the meta-analysis of 16 clinical trials was 1.47. Another strength of the study lies in the modelling of the outcome at two different time-horizons. However, the projection of long-term outcome from the clinical trial data remains problematic, as in the German study.

PROSPECTIVE GERMAN COST-EFFECTIVENESS ANALYSIS

One study has attempted to measure actual costs attributable to alcohol dependence in a real life study comparing standard care alone with standard care using adjuvant acamprosate (Rychlik *et al*., 2001). This German study followed 814 patients over a 1 year period, and documented all medical cost outlay during this period, as well as indirect costs relating to absenteeism and transport to consultations. The open-label study was performed in a naturalistic setting that reflects current standards of the management care of alcohol dependence in Germany. This is an important design feature, because it could be expected that abstinence rates may be lower in such a setting than in the artificial environment of a clinical trial where both physicians and patients are highly motivated, and because sensitivity analyses in all the modelling studies have shown that the abstinence rate is a powerful determinant of the cost-efficiency of acamprosate. In fact, the abstinence rates observed in the study (21.1% in the standard care cohort and 33.6% in the acamprosate cohort) were quite similar to those observed in the randomized clinical trial of acamprosate performed in Germany (Sass *et al*., 1996). This supports a recent report suggesting that abstinence rates are similar in clinical trials and naturalistic settings (Pelc *et al*., 2002), and that the abstinence rates chosen for the base cases of the different modelling studies were appropriate.

Direct medical costs were significantly lower in the acamprosate cohort than in the standard care cohort by €339 in 2004 (€363). These cost savings were generated mainly by a reduced rate of hospitalization (Fig. 4). Indirect costs, principally lost productivity, were also lower in the acamprosate cohort, although this difference (€99; €106) was not statistically significant. However, direct costs contributed 77% of the total costs measured. The cost-effectiveness of standard care was evaluated at €9790 (€10 493 at 2004 values) per abstinent patient compared with a figure of €4857 (€ 5206 at 2004 values) per abstinent patient for acamprosate treatment, a 2-fold difference. Precision estimates were not provided.

This real-world study thus fulfilled the prediction of previous modelling studies that adjuvant pharmacotherapy of alcohol dependence with acamprosate could provide a better clinical outcome at lower cost than could standard care. Although it is difficult to compare the different studies quantitatively, owing to methodological differences, this study based on actual data is most similar to the Belgian modelling study in that both assess short-term cost accrual (12 and 24 months time-frame). In fact, the two studies provide quite similar estimates of cost-savings attributable to acamprosate (the estimate of the real-life study being ~25% higher than that of the Belgian modelling study). However, an important difference between the studies is that acamprosate acquisition costs are accrued over the entire 1 year study period of the

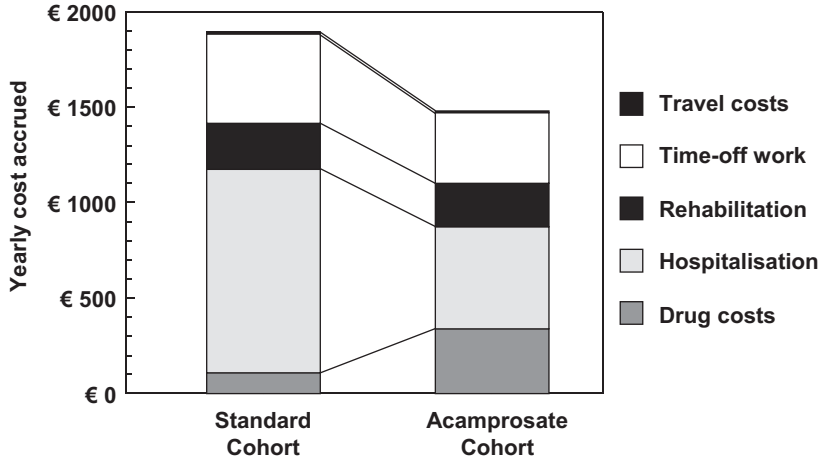

Fig. 4. Cost breakdown for 1 year direct medical costs in patients receiving standard care or standard care with adjuvant acamprosate treatment. Data are taken from the prospective cohort study by Rychlik *et al*. (2001).

German study, but only over the first half of the 2 year Belgian study. Moreover, the modelling study restricted analysis to costs associated with relapse and liver pathology, whereas the real-life study measured all costs that actually occurred. Both of these factors would be expected to lead to an underestimate of the cost savings in the Belgian study, compared with real-world conditions.

STRENGTHS AND WEAKNESSES

The information available on the cost-efficiency of acamprosate has a number of strengths and weaknesses. The principal strength relates to the robustness of the findings, which is indicated by a number of observations. The results of all the studies are coherent, providing a consistent finding that the use of acamprosate provides better outcomes at lower cost (Table 3). All these studies have shown acamprosate use to be a dominant treatment strategy. Furthermore, the results of the prospective cohort study performed in Germany have borne out the predictions of the modelling studies.

The sensitivity analyses performed in all the modelling studies have demonstrated that the cost-efficiency of acamprosate is critically dependent on the abstinence rates achieved with acamprosate. Since the Markov models used data from only two clinical trials (Sass *et al*., 1996; Whitworth *et al*., 1996), it is important to verify that the abstinence rates demonstrated in these studies are representative, which can be done easily by comparing data from all acamprosate published clinical trials. Nonetheless, the abstinence rates obtained in randomized clinical trials may not be representative of those that can be achieved in the routine care of alcohol dependent patients owing to the somewhat artificial conditions of the clinical trials (restrictive inclusion criteria, aggressive follow-up, motivated patients and investigators, etc.). This was first assessed in a large open-label study conducted in five European countries (Pelc *et al*., 2002), which demonstrated that the abstinence rates obtained in naturalistic treatment settings were similar to those reported in the randomized clinical trials. Similarly, in the real-life pharmacoeconomic study performed in Germany (Rychlik *et al*., 2001), abstinence rates very similar to those in the German randomized clinical trial were obtained (Sass *et al*., 1996) (Table 4). Subsequently, a comparative naturalistic study performed in France compared outcome after alcohol detoxification using 'standard care' alone and using 'standard care' with acamprosate (Kiritzé-Topor *et al*., 2004). The treatment effect size in this study was commensurate with that observed in the meta-analysis of the randomized placebo-controlled clinical trials performed with acamprosate (Mann *et al*., 2004). Therefore, it can be concluded that the abstinence rates used in the pharmacoeconomic modelling studies, are appropriate and representative of standard care.

The principal weakness of the information available is the narrowness of the costing source database. Three of the five studies have used German costings, and it is important to extend these findings to countries where the health care cost structure, or the price of acamprosate, are different. Moreover, all the studies have demonstrated that hospitalization costs are the principal determinant of the cost-efficiency of acamprosate. Second, the long-term estimates should be interpreted with caution, since we have no data on long-term outcome from acamprosate beyond 2 years. However, one of the German Markov models evaluated a scenario where the treatment benefit with acamprosate on abstinence was lost after 2 years, and concluded that acamprosate treatment was still a cost-saving strategy in this case (Palmer *et al*., 2000). In the Markov models, an assumption of no post-treatment relapse has been made, but there is no direct evidence available from long-term follow-up studies to support this. Furthermore, little data is available on the impact of acamprosate on indirect costs and savings. These are known to be high, and American data have suggested that indirect costs in family members could actually outstrip direct costs in alcohol-dependent subjects themselves (Holder and Hallan, 1986). Finally, although sensitivity analyses address the issue of robustness of the data, most of the studies provide no explicit measure of the precision of the cost estimates. This hinders comparison of the studies and notably precludes using meta-analysis to attempt to compare cost savings across health care systems.

Table 3. Cost savings per treated patient attributable to acamprosate use

	Direct costs	Indirect costs
Schädlich and Brecht, 1998 Germany	€1450/life	Not determined
Annemans *et al*., 2000 Belgium	€291/year	Not determined
Palmer *et al*., 2000 Germany	€983/life	Not determined
Portella *et al*., 1998 Spain	Not provided	Not provided
Rychlik *et al*., 2001 Germany	€363/year	€106/year

Costs are adjusted for inflation to 2004 values.

Table 4. Abstinence rates observed in clinical studies with acamprosate

Study	Country	Treatment period	Placebo (%)	Acamprosate (%)	Ratio
Sass *et al*., 1996	Germany	1 year	17.3	39.9	2.31
Whitworth *et al*., 1996	Austria	1 year	7.4	18.3	2.47
Portella *et al*., 1998	10 EU	1 year	22.2	29.1	1.31
Rychlik *et al*., 2001	Germany	1 year	21.1[a]	33.6	1.59
Pelc *et al*., 2002	5 EU	6 months	ND	24.4	ND

ND, not determined; EU, European Union.
[a] This was an open label-study where the group being compared received standard care only.

DIRECTIONS FOR FUTURE RESEARCH

The pharmacoeconomic database for acamprosate could usefully be extended to a number of new areas of research. Most importantly, the source data for the clinical benefit of acamprosate and for health care costs needs to be extended to countries where the management of alcohol dependence is different. At the moment, the clinical data used in the modelling studies have come from two countries (Germany and Austria) and the cost data from three (Germany, Belgium, and Spain). The conclusions of the pharmacoeconomic analysis for Germany can be considered robust, but it would be useful to know whether they can be transposed to health care systems where funding is assured by private insurance rather than by national social security, such as in the US. In the US, and many other countries, inpatient detoxification is less widely used than in Germany; because hospitalization is a major component of the cost savings attributed to acamprosate, it would be important to verify that the cost-efficiency of acamprosate is maintained in health care systems where hospitalization for alcohol dependence is less frequent.

The currently available pharmacoeconomic data have been obtained from studies built on the hypothesis that the effect of acamprosate is to increase the probability of achieving abstinence. However, in everyday practice, potential outcomes encompass not only abstinence and relapse, but also a reduction in drinking compared with pre-treatment levels. Since the direct medical costs of alcohol dependence are closely associated with the severity of dependence (McKenna *et al*., 1996), such an outcome would be expected to result in cost savings. Acamprosate has indeed been demonstrated to reduce alcohol consumption in subjects included in the acamprosate clinical trial programme (Chick *et al*., 2003). This point is particularly important in order to evaluate acamprosate treatment strategies where the drug is used without a prior formal detoxification, such as was used in the North American clinical trial of acamprosate (Mason, 2001).

The long-term economic impact of acamprosate treatment has been modelled assuming that abstinence rates observed at the end of the observation periods of clinical trials (2 years) are sustained, and this assumption merits validation. Because acamprosate has now been available in certain countries for over 10 years, it should be possible to address this issue through analysis of long-term outcome recorded in patient registries.

Little information is available on the impact of acamprosate on the indirect costs of alcohol dependence. Since these outweigh direct costs, this impact may be significant. A recent observational study (Kiritzé-Topor *et al*., 2004) has demonstrated that acamprosate reduces the social consequences of alcohol dependence as measured with the Alcohol-Related Problems Questionnaire (Chick *et al*., 1991; Patience *et al*., 1997). This scale quantifies a number of non-medical consequences of alcohol dependence, such as legal, professional, or family problems. Such an approach may be suitable for quantifying the impact of acamprosate on the indirect costs of alcohol dependence.

It would also be useful to compare the cost-efficiency of treatment using acamprosate with that of other pharmacological adjuvant treatments used in the rehabilitation of alcohol-dependent patients, such as naltrexone or disulfiram, for neither of which any pharmacoeconomic data has been published. The ongoing COMBINE study in the US (The COMBINE Study Research Group, 2003) that compares treatment with acamprosate, naltrexone, or both combined with different levels of psychosocial intervention, may provide the necessary outcome data to perform a comparative modelling study of the cost-effectiveness of naltrexone and acamprosate.

Finally, the data on acamprosate could usefully be completed with cost-utility studies in which adjustments are made for changes in the quality of life. Since other studies have indeed demonstrated that acamprosate treatment improves the poor quality of life observed in alcohol-dependent patients (Morgan *et al*., 2004), pharmacoeconomic studies addressing cost-utility would be expected to reinforce the economic argument for using acamprosate.

CONCLUSIONS

There is an extensive body of pharmacoeconomic data relating to the use of acamprosate in the treatment of alcohol dependence. This has included short-term and long-term modelling studies, as well as one prospective real-life study. All these studies have produced consistent results, showing the use of acamprosate to improve clinical outcome and reduce the total costs of treatment and thus be dominant over other rehabilitation strategies not involving pharmacotherapy with acamprosate. In consequence, treatment with acamprosate is highly attractive from a health economics point of view. The principal driver on the reduction of costs is reduced hospitalization. Although there is a short-term increase in treatment costs associated with drug acquisition, these are recovered from long-term savings attributable to reduced hospitalization and rehabilitation costs. Savings in direct medical costs alone outweigh acquisition costs but cost savings accrue both in direct and indirect costs. The funding of the treatment of alcohol dependence by acamprosate is thus both economically and clinically justified for health care payers.

REFERENCES

Annemans, L., Vanoverbeke, N., Tecco, J. *et al*. (2000) Economic evaluation of Campral (Acamprosate) compared to placebo in maintaining abstinence in alcohol-dependent patients. *European Addiction Research* **6**, 71–78.

Briggs, A. and Sculpher, M. (1998) An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics* **13**, 397–409.

Chick J., Lehert P. and Landron, F. (2003) Does acamprosate improve reduction of drinking as well as aiding abstinence? *Journal of Psychopharmacology* **17**, 397–402.

Chick, J., Rund, D. and Gilbert, M. A. (1991) Orthopaedic trauma in men: the relative risk among drinkers and the prevalence of problem drinking in male orthopaedic admissions. *Annals of the Royal College of Surgeons England* **73**, 311–314.

COMBINE Study Research Group (2003) Testing combined pharmacotherapies and behavioral interventions in alcohol dependence: rationale and methods. *Alcoholism: Clinical and Experimental Research* **27**, 1107–1122.

Finney, J. W. and Monahan, S. C. (1996) The cost-effectiveness of treatment for alcoholism: a second approximation. *Journal of Studies on Alcohol* **57**, 229–243.

Gual, A. and Lehert, P. (2001) Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. *Alcohol and Alcoholism* **36**, 413–418.

Hein, R. and Salomaa, J. (1999) What are the costs of substance abuse? Alcohol and drugs. *Alcologia* **11**, 135–143.
Holder, H. D. (1987) Alcoholism treatment and potential health cost saving. *Medical Care* **25**, 52–71.
Holder, H. D. and Blose, J. O. (1991) Typical patterns and cost of alcoholism treatment across a variety of populations and providers. *Alcoholism: Clinical and Experimental Research* **15**, 190–195.
Holder, H. D. and Blose, J. O. (1992) The reduction of health care costs associated with alcoholism treatment: a 14-year longitudinal study. *Journal of Studies on Alcohol* **53**, 293–302.
Holder, H. D., Cisler, R. A., Longabaugh, R. *et al*. (2000) Alcoholism treatment and medical care costs from Project MATCH. *Addiction* **95**, 999–1013.
Holder, H. D. and Hallan, J.B. (1986) Impact of alcoholism treatment on total health care costs: a six year study. *Advances in Alcohol and Substance Abuse* **6**, 1–15.
Holder, H. D., Longabaugh, R., Miller, W. R. *et al*. (1991) The cost effectiveness of treatment for alcoholism: a first approximation. *Journal of Studies on Alcohol* **52**, 517–540.
Kiritzé-Topor, P., Huas, D., Rosenzweig, C. *et al*. (2004) A pragmatic trial of acamprosate in the treatment of alcohol dependence in primary care. *Alcohol and Alcoholism*, in press.
Mann, K., Lehert, P. and Morgan, M. Y. (2004) The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. *Alcoholism: Clinical and Experimental Research* **28**, 51–63.
Mann, K. (2004) Pharmacotherapy of alcohol dependence: a review of the clinical data. *CNS Drugs* **18**, 485–504.
Mason, B. J. (2001) Results of the multicenter study of acamprosate in the treatment of alcoholism. *Biological Psychiatry* **48** (Suppl. 8), 77S (abstract).
McKenna, M., Chick, J., Buxton, M. *et al*. (1996) The SECCAT survey: 1. The costs and consequences of alcoholism. *Alcohol and Alcoholism* **31**, 565–576.
Morgan, M. Y., Landron F. and Lehert, P. (2004). Improvement in quality of life after treatment for alcohol dependence with acamprosate and psychosocial support. *Alcoholism: Clinical and Experimental Research* **28**, 64–77.
Palmer, A.J., Neeser, K., Weiss, C. *et al*. (2000) The long-term cost effectiveness of improving alcohol abstinence with adjuvant acamprosate. *Alcohol and Alcoholism* **35**, 478–492.
Patience, D., Buxton, M., Chick, J. *et al*. (1997) The SECCAT survey: II. The alcohol-related problems questionnaire as a proxy for resource costs and quality of life in alcoholism treatment. *Alcohol and Alcoholism* **32**, 79–84.
Pelc, I., Ansoms, C., Lehert, P. *et al*. (2002) The European NEAT program: an integrated approach using acamprosate and psychosocial support for the prevention of relapse in alcohol-dependent patients with a statistical modeling of therapy success prediction. *Alcoholism: Clinical and Experimental Research* **26**, 1529–1538.
Portella, E., Ridao, M., Carrillo, E. *et al*. (1998) El alcohol y su abuso: impacto socioeconómico. Editorial Médica Panamericana, Madrid.
Reynaud, M., Gaudin-Colombel, A. F. and Le Pen, C. (2001) Two methods of estimating health costs linked to alcoholism in France (with a note on social costs). *Alcohol and Alcoholism* **36**, 89–95.
Rychlik, R., Siedentop, H., Pfeil, T. *et al*. (2001) Cost-effectiveness of adjuvant treatment with acamprosate in maintaining abstinence in alcohol dependent patients. *European Addiction Research* **9**, 59–64.
Sass, H., Soyka, M., Mann, K. *et al*. (1996) Relapse prevention by acamprosate: results from a placebo controlled study in alcohol dependence. *Archives of General Psychiatry* **53**, 673–680.
Schädlich, P. K. and Brecht, J. G. (1998) The cost effectiveness of acamprosate in the treatment of alcoholism: economic evaluation of the Prevention of Relapse with Acamprosate in Management of Alcoholism (PRAMA) Study. *Pharmacoeconomics* **13**, 719–730.
Whitworth, A. B., Fischer, F., Lesch, O. M. *et al*. (1996) Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. *Lancet* **347**, 1438–1442.
Zook, C. J. and Moore, F. D. (1980) High cost users of medical care. *The New England Journal of Medicine* **302**, 996–1002.