Modelling lifetime QALYs and health care costs from different drinking patterns over time: a Markov model

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Abstract

The negative health consequences of alcohol use and its treatment account for significant health care expenditure worldwide. Long-term modelling techniques are developed in this paper to establish a link between drinking patterns, health consequences and alcohol treatment effectiveness and cost-effectiveness. The overall change in health related quality and quantity of life which results from changes in health-related behaviour is estimated. Specifically, a probabilistic lifetime Markov model is presented where alcohol consumption in grams of alcohol per day and drinking history are used for the categorization of patients into four Markov states. Utility weights are assigned to each drinking state using EQ-5D scores. Mortality and morbidity estimates are state, gender and age specific, and are alcohol-related and non-alcohol-related. The methodology is tested in a case study. This represents a major development in the techniques traditionally used in alcohol economic models, in which short-term costs and outcomes are assessed, omitting potential longer term cost savings and improvements in health related quality of life. Assumptions and implications of the approach are discussed. Copyright © 2010 John Wiley & Sons, Ltd.

Introduction

The use of alcohol is one of the leading contributors to ill-health and premature deaths, ranking fifth in the World Health Organization (WHO) list of avoidable risks for Disability Adjusted Life Years (DALYs) (Ezzati *et al.*,

2004; WHO, 2002). A recent analysis of the burden of disease in the European region 2002 has shown that alcohol consumption was causally related to 6.1% of all the deaths, 12.3% of all Years of Life Lost (YLL) and 10.7% of all DALYs (Rehm *et al.*, 2006b). In addition to being a drug of dependence, alcohol is a cause of some 60

different diseases and conditions with short- and long-term health consequences (Room *et al.*, 2005). The extent of some of these consequences is determined not just by the amount of alcohol consumed but also by its consumption pattern, i.e. the frequency and setting of drinking (Rehm *et al.*, 2003a). The physical, psychological and social harms of excessive alcohol use represent an important public health problem and treating alcohol attributable disease accounts for significant health care expenditure. The estimated social costs of alcohol are considerable. For the European Union (EU), United States and Canada these were estimated to be around €270 billion (2003 prices) (Anderson and Baumberg, 2005), US\$185 billion (1998 prices) (WHO, 2004), and CAN\$14.6 billion (2002 prices) (Rehm *et al.*, 2006a), respectively.

Decision-makers have increased the use of cost-effectiveness analysis to determine what interventions will be reimbursed from collective funding (Taylor *et al.*, 2004), where both costs and effects are taken into account. There is an evidence base both on the individual effectiveness of different alcohol interventions (prevention, treatment and enforcement) based on short-term drinking and health outcomes (Raistrick *et al.*, 2006) and on the epidemiological risks associated with different patterns of drinking over time (Rehm *et al.*, 2003b). However, the variety of alcohol treatment approaches and the complexity and multiplicity of treatment outcomes have created a lag in the advance of economic analysis of alcohol treatment. This contribution is concerned with the methodological development of a tool to assess the cost-effectiveness of alcohol treatments. Alcohol consequences may be difficult to measure in a prospective study due to an insufficient follow-up time. Therefore, determining the cost-effectiveness and predicting population outcomes of different alcohol treatments requires modelling of the long-term consequences of changing drinking patterns.

Reviewing published economic models for the assessment of alcohol treatments reveals that this literature is dominated by studies exclusively based on premature mortality outcomes, usually from those abstinent from drinking after an intervention and do not attempt to model the natural flow of patients with alcohol problems (for details on each individual study that used modelling techniques see Corry *et al.*, 2004; Doran *et al.*, 2004; Gentilello *et al.*, 2005; Lindholm, 1998; Palmer *et al.*, 2000; Schadlich and Brecht, 1998; Wutzke *et al.*, 2001). In addition, only one study with modelling techniques (Mortimer and Segal, 2005) presents Quality Adjusted Life Years (QALYs), but these are based on disability weights taken from the literature rather than observed data (Stouthard *et al.*, 2000).

The present contribution extends the previous economic evaluation models of alcohol treatment by: (1) exploring levels of drinking rather than whether people are abstinent or not; (2) providing a dynamic model that allows for relapse and natural recovery; (3) including mortality, morbidity, Health Related Quality of Life and long term costs savings; (4) considering a wider population with alcohol problems, not just those confined to an alcohol dependent population.

The framework presented in this paper allows assessing the cost-effectiveness of alcohol treatments that have the potential to change drinking behaviour. When comparing at least two alcohol treatments, the incremental costs, life years and QALYs come as a result of the analysis and subsequent decisions about treatment choice can be made. Within a decision-making framework, in a circumstance of no uncertainty, the more effective and less costly alcohol treatment should be adopted. In this case the treatment is said to dominate the alternative and the decision of which treatment to adopt is straightforward. However, costs, effects and cost-effectiveness are not known with certainty and this is embedded in the developed model.

This paper describes a method to build a decision analytical model that simulates the drinking patterns of a cohort over lifetime. An application of the model is also presented. The model will have the potential to provide essential information regarding the cost-effectiveness of alcohol treatments and which treatments represent better value for money, as well as to promote consistency and uniformity on economic evaluations of alcohol treatment.

Methods

A Markov model using the cohort simulation approach was built. The main outcome measures are QALYs and lifetime costs. We start by presenting the general Markov structure. This is followed by a description of the epidemiological data required by the model and of the outcomes generated. An explanation of how the model deals with uncertainty and heterogeneity is then provided.

Markov model structure

A Markov model was adopted (Sonnenberg and Beck, 1993) due to its ability to model recurrent events and mortality, which is an ongoing risk over time. The Markov model of alcohol consumption was built in Microsoft Excel® and is presented in Figure 1 (for information on modelling techniques see Briggs *et al.*, 2006).

Figure 1 Markov state transition model.

The Markov model used the cohort simulation approach examining the proportion of a population undergoing different events with associated costs and outcomes (Briggs and Sculpher, 1998; Sonnenberg and Beck, 1993). A hypothetical cohort of patients is modelled through the cycles according to the transition probabilities for each drinking category. The Markov health states (represented by ovals in Figure 1) were defined as mutually exclusive states of drinking behaviour in the form of alcohol consumption. This structure is consistent with alcohol drinking behaviour as a recurrent behaviour with susceptibility for relapse. The drinking process cannot be modelled as a standard chronic disease because patients can move to more serious drinking groups and can also move from more serious drinking levels to less serious ones. Grams of alcohol per day (g/day) were used for the categorization of patients into four Markov states as this allows following a cohort of individuals through their lifetime. Such a measure makes clinical data comparable as different standard units can be converted when calculating alcohol per day. Possible transitions between the states are shown by the arrows in Figure 1. The 'death' state is an absorbing state since patients who transit to this state obviously cannot leave it. Arrows leading from a state to itself indicate that the patient may remain in that state in consecutive cycles. Only certain transitions are allowed. For example, a transition from Harmful to Ex-Hazardous is not allowed. Transition probabilities were assigned for the flow of patients between these drinking states over a discrete time period known as the 'Markov cycle'.

A lifetime horizon was adopted in order to account for the potential of alcohol treatment on improving alcohol-

related mortality and long-term morbidity through a change in drinking behaviour. Evaluation of alcohol treatments on a short term would seriously underestimate expected health outcomes and overestimate costs and uncertainty, since the benefits of alcohol treatment can be expected to accumulate over a much longer period of time.

A one-year cycle length was chosen for the following two reasons: (1) reduction of the complexity of the model as a monthly cycle length, for example, would result in a 12-fold increase in evaluation time over a yearly cycle length (Sonnenberg and Beck, 1993), and (2) lack of lifetime drinking behaviour data for shorter time intervals. In addition, in the natural course of alcohol dependence states do not usually fluctuate on a monthly basis (Dawson *et al.*, 2007).

Markov states as drinking categories

Four drinking categories were defined and these were: Hazardous, Harmful, Ex-Hazardous and, Ex-Harmful. Patients to which the treatments under analysis are delivered start the model in two categories according to the proportion in each one of the categories at baseline, for the country where the study takes place. The drinking categories by gender, defined in grams of alcohol consumed per day, in cycle zero are the following two:

- (1) Hazardous drinking: ≤ 54.99 g/day (women); ≤ 79.99 g/day (men)
- (2) Harmful drinking: ≥ 55 g/day (women); ≥ 80 g/day (men)

In cycle one and following cycles ($n + 1$), patients can be in one of the following five categories:

- (1) Hazardous drinking: 20–54.99 g/day (women); 28–79.99 g/day (men)
- (2) Harmful drinking: ≥ 55 g/day (women); ≥ 80 g/day (men)
- (3) Ex-hazardous drinking: < 20 g/day (women); < 28 g/day (men) and hazardous drinking in previous cycle
- (4) Ex-harmful drinking: < 20 g/day (women); < 28 g/day (men) and harmful drinking in previous cycle
- (5) Death: patient is dead

As women often experience higher risks of disease and injury for less volume of consumption, the respective drinking categories for women had lower means (Rehm *et al.*, 2007). The definition of the harmful drinking category was based on the definition of 'drinking category III' presented by the WHO (Rehm *et al.*, 2004b). The limits used to define the 'Ex-categories' were based on the

definition of 'sensible drinking' presented in the National Alcohol Strategy for England (Department of Health, 2007b). Hazardous drinking in cycle zero was solely defined by an upper bound which, at first instance, might seem like a lapse. This was not the case, and such interval was assumed so that patients drinking at 'sensible drinking' at baseline could also undertake alcohol treatment. It might be the case that those patients drinking at lower levels at baseline were actually drinking at higher levels before the assessment point for treatment deliver and are still at risk for alcohol-related diseases and, therefore, are eligible for treatment given their past history and susceptibility for relapse. The 'Ex-categories' were defined similarly in terms of alcohol per day as the only thing distinguishing them is the state where the patient was in the previous cycle (Hazardous or Harmful or any of the two Ex-states), for patient history can influence the risk of death and morbidity. This breakdown is related to the fact that, even if patients reduce their alcohol consumption to a sensible level, the risk of mortality and morbidity will partly depend on the level at which they were drinking before.

A generic transition matrix presenting the transitions between Markov states and associated probabilities is presented in Table 1.

The transition matrix in Table 1 specifies the generic transitions between drinking categories for any given cycle of the model. The cohort-based transition matrix uses a transition probability per unit time for individuals in the cohort to change to another state, with associated costs and outcomes. The rows of the transition matrix must add to one (a conservation of probability mass). The transition matrix presented shows that transitions

between some model states are not allowed. Probabilities representing disallowed transitions are zero. The transition probabilities are constant with respect to time, with the exception of the transitions to the death state that are age-dependent. When modelling, the probability of remaining in one state will depend on the probability of leaving that same state, where the age-dependent transition to the death state are taken into account, making therefore the overall probability of remaining in a particular state time-dependent.

Transition probabilities for the first cycle(s)

Yearly transition probabilities for each state are used to generate the Markov trace. Transition probabilities for the study informing the effectiveness of the alcohol treatments under analysis can be calculated through counting the individuals that moved between the drinking categories previously defined. These probabilities are only used for the number of cycles of the model that the data informs. Most effectiveness studies in the alcohol treatment field have not surpassed one year follow-up (Miller and Wilbourne, 2002). Therefore, data from these studies should only be used for the first cycle of the model.

Transition probabilities for the following cycles

It would be a strong assumption to use the transition probabilities taken from the effectiveness data for patients' lifetime, i.e. for the cycles of the model following treatment. When treatment effects are taken from a clinical trial, which rarely measure outcomes beyond one year, it is recommended that shorter and longer time horizons are modelled separately when the analysis must go beyond

Table 1 Generic transition matrix for the Markov model of alcohol behaviour

Cycle <i>n</i>	Cycle <i>n</i> + 1				
	Hazardous (A)	Harmful (B)	Ex-Hazardous (ExA)	Ex-Harmful (ExB)	Death (D)
Hazardous (A)	tpA2A	tpA2B	tpA2ExA	0	tpA2D ¹
Harmful (B)	tpB2A	tpB2B	0	tpB2ExB	tpB2D ¹
Ex-Hazardous (ExA)	tpExA2A	tpExA2B	tpExA2ExB	0	tpExA2D ¹
Ex-Harmful (ExB)	tpExB2A	tpExB2B	0	tpExB2ExB	tpExB2D ¹
Death (D)	0	0	0	0	1

¹ Time-dependent transition probability.

Note: tp, transition probability; tpA2A, transition probability from hazardous to hazardous; tpB2A, transition probability from harmful to hazardous; tpExA2A, transition probability from ex-hazardous to hazardous; tpExB2A, transition probability from ex-harmful to hazardous. Example: a Hazardous patient can remain in Hazardous, transit to Harmful, transit to Ex-Hazardous or transit to Death.

the time frame of the primary data (Gold *et al.*, 1996). The transition probabilities for the following cycles are, therefore, specific to the country where the study takes place, so that the drinking behaviour of a specific population, after treatment uptake, can be reflected upon patients' lifetime. These transitions are informed by long-term follow-up data.

Epidemiological data: morbidity and mortality

By attaching estimates of resource use and health consequences to each individual state in the model over a large number of cycles, the long-term costs and health consequences can be estimated. However, in order to do so, the Markov model requires a separate analysis of the lifetime risk of mortality and morbidity that is incorporated into the main Markov model to reflect the risk incurred by each drinking state and the changing risk of transitioning into or out of drinking states. Lifetime injury and chronic disease mortality and morbidity are modelled through a number of different steps, assumptions and data sources [please see Taylor *et al.* (2008) and Rehm *et al.* (2008) for a discussion of the model and its assumptions]. Briefly, after determination of diseases and injury groups causally related to alcohol consumption (Rehm *et al.*, 2004a), consumption-specific alcohol-attributable fractions are developed based on country-specific alcohol consumption prevalence and relative risks for each age, sex, and disease/injury category. These are combined with numbers of drinks and number of drinking occasions (for injury risk calculation) or volume of alcohol consumed (for chronic disease risk calculation) by drinkers characterized by each drinking state over the course of one year to determine a one-year lifetime alcohol-attributable risk for each disease/injury group by sex, age, and drinker type. These risks are then accumulated over time, through the Markov model, to calculate a final attributable risk of mortality/morbidity for injury/chronic disease, respectively. This risk therefore reflects actual consumption patterns of the drinking states being modelled in a population of interest, in terms of mortality/morbidity experience, alcohol consumption, and risk per occasion.

Model outcomes

The outcomes of the model are the years of life, QALYs and lifetime costs and these are specific to the treatments under evaluation and to the country of the analysis. Drinking categories representing a higher level of consumption have associated higher costs, lower utility and an increased probability of dying from alcohol-attributable conditions. *Life expectancy* for the treatments

evaluated is given by the number of cycles (average amount of time) spent in each state, other than the Death state, by the patients. Lifetables for the model states (alcohol-specific) and baseline (general mortality) and by gender and age group are linked to each state, with rates taking into account both chronic and injury causes. The patients alive in each cycle are summed and divided by the initial size of the cohort in order to get the average life expectancy.

QALYs calculation involves weighting the length of time spent in each state of health by a value representing quality of life experienced in that state. Weights representing quality of life on a standard zero to one scale are attached to the Markov states. These weights are called utilities. QALYs are calculated by multiplying the utility weights in each state by the time in the health state. The QALY scores for patients in each cycle are summed over all cycles and divided by the initial cohort size thus providing average QALYs.

The economic model has two major categories of *costs*, the costs of the treatments under evaluation and the disease-related costs. The treatment costs are specific to the alcohol treatments under evaluation and the disease costs are specific to the country and setting where the study takes place. The model was structured in such a way that inputting the costs of alcohol treatments is straightforward. The Markov states costs are calculated by combining the morbidity rates and the average unit costs for the diseases affecting alcohol-attributable morbidity. Specifically identified diseases with alcohol-related morbidity rates by gender, drinking state and for each age group, are used for the calculation of state costs. The lifetime states cost is obtained by summing the costs across all cycles for each state and dividing by the initial cohort size thus providing average states' cost.

Dealing with uncertainty and heterogeneity

Some of the model inputs are not known with certainty. Therefore, the model incorporated uncertainty in its inputs through the use of probabilistic sensitivity analysis (PSA). One-way sensitivity analysis, for a set of input parameters, was also embedded in the structure.

PSA is incorporated in the model by assigning distributions to the input parameters of the model that the results are uncertain about, namely: transition probabilities and states' utilities. Then, Monte Carlo simulation selects values of the parameters from the assigned distributions, at random (Doubilet *et al.*, 1985). One-way sensitivity analysis, where each parameter is varied individually, is incorporated for analysing the impact of

applying a discount rate for costs and health outcomes different from the one assumed in the base-case analysis. One way sensitivity analysis can also be conducted for the initial distribution of patients, where the effect of different proportions of patients starting in hazardous and harmful states is analysed. Markov models assume that all patients in a given state are homogenous and, in order to overcome this, the model can also be run for cohorts of males and females at ages of 20, 40 and 60 years old in order to deal with heterogeneity.

A summary table with the general Markov model characteristics is provided in the Appendix.

Case study: an application of the Markov model of drinking behaviour to UK data

The structure and functionality of the developed Markov model of drinking behaviour were tested using patient-level data from the UK alcohol treatment trial (UKATT Research Team, 2005). The study population of this trial comprised people of all ages above 16 who would normally seek treatment for alcohol problems at a British treatment site. The UKATT consisted on a cost-effectiveness analysis alongside a pragmatic multicentre randomized trial aimed at comparing the cost-effectiveness of Social Behaviour and Network Therapy (SBNT), a new treatment for alcohol problems, with that of the proved Motivational Enhancement Therapy (MET). The UKATT showed that, in the short term, SBNT was more cost-saving and less effective than MET but this difference was not statistically significant. Overall, the trial showed no strong evidence about the effectiveness and cost-effectiveness of the two treatments. Applying the Markov model of drinking behaviour to the UKATT data permits the assessment of the incremental costs, survival and QALYs for MET versus SBNT in the long term.

The model was tested for the UK, using the UKATT patients' data, but can be adapted to any other country of interest. The base-case cohort was a UK male cohort with an average starting age of 40 years old. The cohort of patients was modelled for an 80 year time horizon, by which time all patients were predicted to have died. The model evaluated costs from the perspective of the National Health Service and Personal Social Services (NHS & PSS), expressed in UK pound sterling at a 2007 price base. Both costs and outcomes were discounted using a 3.5% annual discount rate, in line with current NICE guidelines (2004).

The computation of the transition probabilities for the first cycle of the model involved counting the number of MET and SBNT patients in each category, by gender, at

baseline and 12 months, using the statistical software package SPSS.

This case study used a long-term drinking behaviour follow-up study conducted by Taylor *et al.* (1985), as the best information for the following cycle's transitions available until present date. Taylor *et al.* (1985) reported the proportion of patients who remain in a certain drinking status for the following year, over 10 years, using 68 patients who were admitted into a controlled study of treatment versus advice with a one and two years follow-up. The authors' drinking categories were matched to the present model categories and no distinction between Ex-categories was possible as the study did not report the effect of present consumption on following year consumption. Another assumption made was that the probability of transitioning to any other of the two allowed states would be one minus the probability of remaining in the same state, divided by two. The transition matrix used in the model for the following cycles is presented in Table 2.

The transition probabilities used for the following cycles were based on some assumptions, namely: (1) drinking groups as defined in the Taylor *et al.* (1985) study can be matched to the model categories; (2) transitions remain constant over time; (3) transition to the two other states, not informed by the Taylor *et al.* (1985) study, are the same; (4) transitions reported in the study are observed right after the cycles for which clinical effectiveness data is available; (5) transitions do not differ by gender; and (6) once treatment stops, transition rates are assumed to be the same between the compared arms of the model.

Two different distributions were chosen in order to conduct the probabilistic sensitivity analysis. Transition probabilities for the first cycle were estimated from multinomial data and, therefore, assigned the Dirichlet distribution. Transition probabilities for the following cycles and utilities were both derived from binomial data and, therefore, assigned a beta distribution.

UK-specific epidemiological data was retrieved in order to build lifetime tables and to compute alcohol-attributable morbidity rates associated with each Markov state, by gender and age. Lifetables were linked to the model cycle and were used to gauge the life years gained with each therapy. The lifetables used both UK alcohol-specific and general mortality rates (see Table 3).

Morbidity rates were used to estimate the states' costs. The ICD 10 codes (International Classification of Diseases), as provided in the Hospital Episodes Statistics (NHS, 2007b) for the alcohol-related diseases, were converted to Health Care Resource Group (HRG) using an

Table 2 Transition matrix for the following cycles

Cycle <i>n</i>	Cycle <i>n</i> + 1				
	Hazardous (A)	Harmful (B)	Ex-Hazardous (ExA)	Ex-Harmful (ExB)	Death (D)
Hazardous (A)	0.86 ²	0.07	0.07	0	tpA2D ¹
Harmful (B)	0.085	0.83 ²	0	0.085	tpB2D ¹
Ex-Hazardous (ExA)	0.095	0.095	0.81 ²	0	tpExA2D ¹
Ex-Harmful (ExB)	0.095	0.095	0	0.81 ²	tpExB2D ¹

¹Time-dependent transition probability.

²Yearly stability reported in Taylor *et al.* (1985).

Note: tp, transition probability; tpA2D, transition probability from hazardous to death; tpB2D, transition probability from harmful to death; tpExA2D, transition probability from ex-hazardous to death; tpExB2D, transition probability from ex-harmful to death.

Table 3 Lifetable: age-dependent transition probabilities to death for a UK population (per 1000)

Yearly transition mortality probabilities by age and sex for each state and for baseline											
Lifetable		Hazardous		Harmful		Ex-Hazardous		Ex-Harmful		Baseline mortality	
A	A'	M	F	M	F	M	F	M	F	M	F
15–29	15	0.44	0.11	1.01	0.25	0.08	0.04	0.25	0.07	0.27	0.16
30–44	30	0.92	0.42	1.94	0.79	0.39	0.28	0.63	0.35	0.55	0.39
45–59	45	2.95	1.74	5.04	2.76	2.15	1.37	2.50	1.55	2.47	1.78
60–69	60	8.33	4.96	10.46	5.92	7.44	4.58	7.82	4.77	9.21	5.99
70–79	70	23.92	17.28	26.65	18.76	22.59	16.66	23.16	16.94	25.72	15.66
>80	80	62.95	67.81	65.95	70.24	60.86	66.42	61.86	67.10	68.70	48.40

Note: M, males; F, females; A, age; A', age index.

online casemix converter (NHS, 2007a). The national average unit costs were retrieved from the National Schedule of Reference Costs, using elective inpatient HRG data (Department of Health, 2007a; Appendix NSRC1 Aa) and up-rated to 2006/2007 prices, using the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care 2007 (Curtis, 2007). Finally, the unit costs of each disease, as presented in Table 4, were weighted by the correspondent morbidity risk and the sum of the weighted costs of the alcohol-related diseases, by age and gender, were linked to each drinking state.

Health state utilities were retrieved from UKATT (UKATT Research Team, 2005). Patients completed the EQ-5D questionnaire (Williams, 1990) and UK population norms were used to value patients' health states (Kind *et al.*, 1999). For the Markov states' utilities calculation, all UKATT sample ($n = 742$) was used and average utilities were obtained for each state by using the

statistical package SPSS®. The trial data provided 414 patients with EQ-5D values at baseline and 12 months that were allocated to a drinking category according to their level of drinking. Utilities (standard error) for Hazardous, Harmful, Ex-Hazardous and Ex-Harmful states were 0.6597 (0.0258), 0.6349 (0.0245), 0.7001 (0.07591) and, 0.6459 (0.0436), respectively.

The costs of SBNT and MET were taken from the UKATT and up-rated to 2006/2007 prices using the HCHS inflation index (Curtis, 2007). The first cycle of the model used mean net public sector savings for SBNT and MET of £593 (standard deviation 4114) and £798 (standard deviation 3817), respectively.

Table 5 presents a summary of the base-case analysis and three alternative scenarios considered as part of the univariate sensitivity analysis. For each element, the position in the base-case analysis is outlined, alongside the alternative assumption applied.

Table 4 Average unit costs for the alcohol-related diseases

GBD	GBD description	Average unit cost
W061	Oral cavity, pharynx	£1989.68
W062	Oesophageal cancers	£1275.63
W065	Liver cancer	£2138.80
W069	Breast cancer	£1091.27
W086	Alcohol dependence syndrome	£1469.70
W106	Hypertensive disease	£1329.48
W107	Ischemic heart disease (IHD)	£1515.50
W108	Ischaemic and Haemorrhagic stroke	£2345.72
W117	Cirrhosis of the liver	£1961.69

Note: GBD, global burden of disease; 2006/2007 prices, British pounds (£, GBP); conversion between GBD and ICD 10 codes from: <http://www.dcp2.org/pubs/GBD/3/Table/3.A2>.

Table 5 Details of the key elements of the base-case analysis and how these were varied in the univariate sensitivity analysis

Element	Position in base-case analysis	Variation in sensitivity analysis
Population	All males. Average age = 40 years (UKATT Research Team, 2005)	Separate analysis for males and females. Alternative starting ages assumed: 20, 40 and 60 years.
Discount rate	3.5% applied to both costs and outcomes (NICE, 2004)	6% costs, 1.5% outcomes (NICE, 2004)
Cohort distribution at baseline	26% hazardous, 74% harmful (UKATT Research Team, 2005)	50% hazardous, 50% harmful

Case-study results

A measure used in order to determine whether an intervention represents good value for money is the expected incremental cost per QALY (ICER, Incremental Cost Effectiveness Ratio) against a threshold willingness to pay (λ). The ICER compares the additional costs that one strategy incurs over another with the additional benefits and represents the additional cost required to achieve one additional unit of outcome (QALY). In the UK a benchmark of between £20,000 and £30,000 per additional QALY represents acceptable value for money for adoption by the NHS (NICE, 2004).

The importance of a long-term model in the cost-effectiveness analysis of alcohol treatment is reflected in the ICER obtained for each model cycle. The reduction in the ICER as the short-term analysis progresses to a long-term one is depicted in Figure 2. The chart represents the ICER, computed as the cumulative difference in costs and QALYs, for each cycle year. It is shown that after the 27th

cycle MET is potentially cost-effective, achieving an ICER below £30,000/QALY.

The outputs of the PSA, using Monte Carlo simulation, of the alcohol behaviour model provide the distribution over the incremental cost, incremental effect and the joint cost-effect distribution. The mean cost-effectiveness ratio of MET versus SBNT estimated from 1000 random draws is approximately £26,670 per QALY. The simulation results of the overall uncertainty in the model are presented in a cost-effectiveness acceptability curve (CEAC) (Briggs *et al.*, 2006; Briggs and Tambour, 2001). The CEAC derived from the model is presented in Figure 3 where the resulting probability that one therapy is better than the other is plotted against the maximum that decision-makers might pay for an additional QALY. The CEAC shows that the probability that MET is cost-effective cuts the horizontal axis for threshold values below £2500 per QALY, where SBNT is more cost-effective than MET (when thresholds are small, SBNT seems preferable to MET). As the threshold increases and

Figure 2 Incremental cost-effectiveness ratio (ICER) of motivational enhancement therapy (MET) versus social behaviour network therapy (SBNT) per cycle year.

Figure 3 Cost-effectiveness acceptability curve (CEAC) of the probability that motivational enhancement therapy (MET) is cost-effective against threshold of willingness-to-pay.

therefore, health gains are more highly valued, the probability that MET is cost-effective increases, being 0.5 at the value of the ICER (£26,670/QALY), where both treatments have the same probability of being cost-effective. The probability that MET is the most cost-effective therapy is 0.4 and 0.5 for threshold values of £20,000 and £30,000, respectively.

The base-case results were robust when the model was tested via sensitivity analysis on the discount rate, where the alternative discount rates improved the cost-effectiveness by a minor amount. Modelling a cohort equally distributed between the hazardous and harmful categories makes MET treatment considerably more cost-effective (smaller ICER than in base-case: £18,000/QALY versus £27,000/QALY). This can be explained by the fact that a lower proportion of patients in the harmful drinking state represent lower overall costs and higher QALYs. However, when analysing the effect of heterogeneity in

the results, the model showed that SBNT dominates MET for the three simulated age cohorts of females. The gender and age variation in the ICER can be explained by two factors: (1) impact on the numerator of the ICER and therefore on the incremental costs and, (2) impact on the denominator of the ICER and therefore on the incremental effects. Mortality rates, morbidity rates, drinking behaviour and treatment effects by gender and age affect the two aforementioned factors.

Overall, the results of the long-term analysis vary across different subgroups and different treatment decisions should be made for different categories of patients, according to the decision-maker threshold for treatment adoption. Decision-makers may also consider delivering MET to a less severe population instead of a mainly harmful drinking group.

If decision-makers are willing to pay more than £27,000 per QALY gained, then MET should be adopted

for males as it has a higher probability of being cost-effective. The gender differences ought to be further studied, but it appears that SBNT represents better value for money than MET when delivered to females.

Discussion

The described model can be used to produce cost-effectiveness estimates for a range of alcohol treatments. However, it is based on a number of assumptions that should be discussed here. The main assumption in a simple Markov model is that it is essentially without memory. That is, it does not allow one to follow a patient's history. Therefore, time-dependency in the transition probabilities are accounted for only by increasing age but they do not depend on the time patients have actually spent in each state. The use of 'ex-categories' can be seen as away to overcome this lack of memory of a standard Markov model, but not to a full extent. Establishing transition probabilities that depend on the time the individuals spent in each state would require a patient-level simulation (PLS) model. However, the computational burden of PLS models compared with cohort models make PLS less attractive. One-year cycles were used in order to decrease the complexity of the model and also to take into account the level of data availability. However, given the nature of alcohol consumption, it is not expected that individuals remain in the same drinking level for one year and a much shorter cycle length may be appropriate.

The model also assumes that exposure to other alcohol interventions (enforcement and prevention) is the same for the alternative groups in the long run. This is one of the biggest assumptions in the case study, which used long-term follow-up data that did not follow the specific treatments evaluated. Therefore, the outcomes after treatment are the same for a group of patients in the same drinking category and with the same age and sex. In order to take into account the effect of different exposures on drinking behaviour we would need a long-term follow-up study for the specific interventions' groups. In addition, possible interactions between exposures would need to be taken into account.

Markov states' utilities were based on data from the UKATT. However, using utilities taken from the UKATT for the computation of the Markov states' utilities in the model presents some limitations. For example, the trial was UK-based and utilities valuation was that of a UK population which might hamper utilities transferability to other settings. Nevertheless, it is common practice that economic evaluations conducted worldwide use UK

utilities valuation for QALYs calculation. Also, these utilities were generated from the EQ-5D questionnaire which may not include facets of quality of life related to alcohol consumption. The relationship between utility measures and alcohol consumption is a topic for further research.

The case-study application to the UK illustrates potential data limitations to populate the theoretical model. In particular, drinking behaviour after treatment uptake was taken from a longitudinal study with a small sample size and many assumptions were made regarding the application of the study to the model.

The perspective of the case-study analysis was that of the health care system. The public health impact of alcohol, however, is not only experienced by individual drinkers but also by the rest of society. Alcohol consumption increases the risk of social harms, ranging from social nuisances through to more serious consequences such as marital harm, child abuse, drink-driving accidents, loss of work productivity, serious pre-natal conditions, crime, violence and homicide. With a broader perspective, where these social consequences are also taken into account, alcohol treatments may be even more cost-effective due to the large scope for society-level consequences improvement. It would also be interesting to analyse the impact of a societal perspective on the ranking of treatments. Adopting a societal perspective is one of the objectives for further work developing both the theoretical model and empirical applications.

The case study showed that, even when comparing low intensive treatments with very similar effectiveness and costs, the model provides information highly valuable for decision-making. The long-term analysis, incorporating uncertainty, showed that one treatment is better value for money than the other and that different decisions should be done according to the gender of the patients.

Treatment studies involve individuals voluntarily changing behaviour. While much of the content of this paper referred to alcohol treatment, it is possible to adapt the model for other alcohol interventions. Other policies directed at all drinkers whether having problems or not and involving some coercion, e.g. taxation, could be thought of having different individual impacts as well as a social gain. An adaptation of the model as to incorporate different alcohol interventions will be part of future work. An important contribution modelled the population-level impact of a range of interventions (Chisholm *et al.*, 2004).

Despite some of the limitations, which naturally arise when a modelling approach is adopted, the present paper is a major contribution for the link between drinking patterns, health consequences and alcohol treatments

effectiveness and cost-effectiveness. Alcohol has a range of both short- and long-term consequences. However, this may well be difficult to measure in a prospective study with patients. For example, while those continuing drinking hazardingly may frequently drink and drive, the probability of an accident on each individual occasion is low. In addition, only a long-term study can capture the potential gain in life years achieved with a treatment for alcohol problems. Undoubtedly, a modelling approach is paramount to the economic evaluation of alcohol treatment.

This paper provided a framework by which policy-makers can evaluate alcohol treatments taking into account longer term health outcomes and costs. It enables the estimation of benefits from alcohol treatment related to a change in alcohol consumption which is not necessarily confined to abstinence. This represents a major development in the techniques traditionally used in the field of alcohol treatment, in which short-term costs and outcomes are assessed, omitting potential longer term cost savings and improvements in health related quality of life.

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Declaration of interest statement

The authors have no competing interests.

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Appendix

Model structure

Type of model	Markov model
Markov states	Five Markov states were defined: Hazardous drinking (A), Harmful drinking (B), Ex-Hazardous drinking (ExA), Ex-Harmful drinking (ExB) and Death (D).
Time horizon	Lifetime
Cycle length	One year

Model inputs

Population	The model uses the cohort simulation approach. Therefore, a cohort of patients, to whom treatment is delivered, is analysed. A base-case population should be specified. The average age of the patients to which treatment is delivered and the gender with higher proportion of patients can be used for the base case.
Treatment effect	Treatment effect is the change in drinking behaviour, reflected in the flow of patients between the Markov states. This is incorporated in the model through the transition probabilities informed by the clinical study – transition probabilities for the first cycle(s). This parameter is specific to the treatments under evaluation.
Transition probabilities (tp) informed by clinical study	These transitions are informed by the clinical data by counting the number of patients in each drinking category at baseline and follow-up. The number of model cycles informed by the clinical data depends on the duration of the clinical study. The possible transitions are: A2A (remains hazardous); A2B (hazardous to harmful), A2ExA (hazardous to ex-hazardous); A2D (hazardous to death); B2A; B2B; B2ExB; B2D; ExA2A; ExA2B; ExA2ExA; ExA2D; ExB2A; ExB2B; ExB2ExB; ExB2D.
Transition probabilities for the following cycles	These transitions are informed by country-specific data on the drinking behaviour of patients after treatment uptake. The ideal source of data is a longitudinal study that assesses people drinking, after treatment uptake, over a long time period. The possible transitions are the same as for the initial cycle(s).
Mortality rates	This is country specific. Mortality rates have two components: alcohol-specific mortality rates and baseline mortality rates. Alcohol-related mortality rates should be calculated for both injury and chronic diseases causes, by gender, age and drinking category. Baseline mortality rates are age and gender-specific.
Morbidity rates	This is country specific. Morbidity rates should be calculated for both injury and chronic alcohol-related events. These vary by gender, age and drinking category.
Markov state utilities	Utilities attached to each Markov state are country specific. Ideally, the utility associated with each drinking category is estimated using general population valuations and a generic preference-based measure.
Discount rate	The model applies an annual discount rate for costs, life years gained and quality adjusted life years.
<i>Model outcomes</i>	
Years of life	These are calculated by total number of cycles spent in each state, other than the death state. The years of life with each treatment under analysis can be compared and an estimate of the incremental life years gained is computed.
Quality-adjusted life years (QALYs)	These are calculated by multiplying the time in each state by the utility weights and summing over all cycles. The QALYs associated with each treatment under analysis can be compared and an incremental QALY gain is computed.
Lifetime costs	There are two categories of costs: the treatment costs and Markov state costs. The treatment costs are specific to the treatment under evaluation and the Markov state costs are country and setting-specific. The total costs for each treatment can be compared and an incremental cost computed.
<i>Sensitivity analysis</i>	
One-way	The model can incorporate a range of one-way sensitivity analysis. Interesting analysis include analysing the impact on the results of: different discount rate, changes in the cohort gender and age (subgroup analysis), and changes in the proportion starting in hazardous or harmful states.
Probabilistic sensitivity analysis (PSA)	PSA, using Monte Carlo simulation, is incorporated in the model for the input parameters of the model that the results are uncertain about, namely: transition probabilities and utilities.