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The cost-effectiveness and public health benefit of nalmefene added to psychosocial support for the reduction of alcohol consumption in alcohol-dependent patients with high/very high drinking risk levels: a Markov model

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ABSTRACT

Objectives: To determine whether nalmefene combined with psychosocial support is cost-effective compared with psychosocial support alone for reducing alcohol consumption in alcohol-dependent patients with high/very high drinking risk levels (DRLs) as defined by the WHO, and to evaluate the public health benefit of reducing harmful alcohol-attributable diseases, injuries and deaths.

Design: Decision modelling using Markov chains compared costs and effects over 5 years.

Setting: The analysis was from the perspective of the National Health Service (NHS) in England and Wales.

Participants: The model considered the licensed population for nalmefene, specifically adults with both alcohol dependence and high/very high DRLs, who do not require immediate detoxification and who continue to have high/very high DRLs after initial assessment.

Data sources: We modelled treatment effect using data from three clinical trials for nalmefene (ESENSE 1 (NCT00811720), ESENSE 2 (NCT00812461) and SENSE (NCT00811941)). Baseline characteristics of the model population, treatment resource utilisation and utilities were from these trials. We estimated the number of alcohol-attributable events occurring at different levels of alcohol consumption based on published epidemiological risk-relation studies. Health-related costs were from UK sources.

Main outcome measures: We measured incremental cost per quality-adjusted life year (QALY) gained and number of alcohol-attributable harmful events avoided.

Results: Nalmefene in combination with psychosocial support had an incremental cost-effectiveness ratio (ICER) of £5204 per QALY gained, and was therefore cost-effective at the £20 000 per QALY gained decision threshold. Sensitivity analyses showed that the conclusion was robust. Nalmefene plus psychosocial support led to the avoidance of 7179 alcohol-attributable diseases/injuries and 309 deaths per 100 000 patients compared to psychosocial support alone over the course of 5 years.

Conclusions: Nalmefene can be seen as a cost-effective treatment for alcohol dependence, with substantial public health benefits.

Strengths and limitations of this study

- This cost-effectiveness analysis employed an innovative approach towards modelling the treatment of alcohol dependence using WHO drinking risk levels and abstinence as health states.
- The analysis also used an innovative approach for modelling the incidence of alcohol-attributable harmful events.
- This analysis is based on 1-year clinical trial data assessing nalmefene, extended to a time horizon of 5 years as appropriate for a chronic disease using data from the literature and clinical experts' advice. Simplifications of certain modelling features when extrapolating patients' trajectories after the trial time horizon represent limitations of the decision model.
- The exploratory 'no treatment' arm used to assess the public health benefit of patients beginning treatment for alcohol dependence may not be an accurate representation of the natural evolution of the disease when untreated. The results from this analysis should not be taken at face value but seen as a broad estimation of the benefit of patients entering treatment for alcohol dependence.
- The generalisability of this study to the UK population may be suboptimal, owing to the fact that the nalmefene clinical trials were multinational. Furthermore, the use of quality-adjusted life years (QALYs) derived from these trials may not have fully captured the effectiveness of nalmefene.

Trial registration numbers: This cost-effectiveness analysis was developed based on data from three randomised clinical trials: ESENSE 1 (NCT00811720), ESENSE 2 (NCT00812461) and SENSE (NCT00811941).

INTRODUCTION

The physical, psychological and social harms of alcohol consumption represent an important public health problem and impose substantial costs on society.[1 2] Alcohol consumption is associated with an increased risk of disability and mortality, due to the development of diseases linked with alcohol consumption including liver cirrhosis, certain cancers and cardiovascular diseases and alcohol-related injuries such as falls and automobile accidents.[3 4] Given that most dose–response curves for alcohol consumption on disease and injury outcomes are exponential, heavy drinking, both episodic and chronic, plays a major role in creating this disease burden.[5 6] In Europe it has been estimated that more than two-thirds of overall premature adult mortality (ages 15–64) is due to heavy drinking.[7] As alcohol use disorders, especially alcohol dependence, are closely linked to heavy drinking occasions, the majority of premature mortalities in the aforementioned study were a result of alcohol-attributable disorders.[7] High levels of alcohol consumption can also prove economically costly through treatment costs, productivity losses and losses due to alcohol-related crime and accidents.[2 8]

While historically the National Institute for Health and Care Excellence (NICE) has recommended interventions to promote abstinence from alcohol, harm reduction by lowering alcohol consumption is now recognised as a valid objective in the treatment of alcohol dependence.[8 9] The European Medicines Agency (EMA) has outlined two types of clinical trial for alcohol dependence treatments: 'relapse prevention' trials and 'harm reduction' trials.[10] 'Relapse prevention' trials are suitable for agents such as acamprosate and naltrexone, of which the purpose is to promote sustained abstinence after successful detoxification. 'Harm reduction' trials are suitable for agents aiming to lower alcohol consumption levels in patients who are non-abstinent at trial randomisation.

Nalmefene is the first pharmacological treatment licensed in the European Union (EU) to achieve reduction of alcohol consumption.[11] It is an opioid system modulator with a distinct μ, δ and κ receptor profile, and by modulating the effect of alcohol on the cortico-mesolimbic system it is thought to reduce the reinforcing effects of alcohol, thereby helping patients to reduce their level of consumption.[12 13] Nalmefene is indicated in the EU, in conjunction with psychosocial support, for alcohol-dependent adult patients who are both alcohol-dependent and who also have a high/very high drinking risk level (DRL) as defined by the WHO (table 1). In addition, it is indicated only for patients without physical withdrawal symptoms and those who do not require immediate detoxification. It should be initiated only in patients who continue to have a high/very high DRL 2 weeks after initial assessment, in line with the patient population included in three phase III clinical trials of nalmefene: ESENSE 1 (NCT00811720), ESENSE 2 (NCT00812461) and SENSE (NCT00811941).[14 15] These trials demonstrated the clinical efficacy of nalmefene in its licensed population in terms of reducing the number of heavy drinking days (HDDs) per month and daily total alcohol consumption (TAC). Based on dosing used in these trials, nalmefene should be taken on an as-needed basis each day that the patient perceives a risk of drinking alcohol, with a maximum dose of one tablet per day.[11]

The relevance of reducing alcohol consumption, as opposed to promoting complete abstinence, has been a key focus of discussions in the UK surrounding the possible introduction of minimum pricing of alcohol. The principle behind this proposal is that increasing the cost of purchasing alcohol may reduce the level of alcohol consumption in harmful drinkers, which may in turn have a meaningful impact on reducing alcohol-related harms and burden.[17] In Scotland, research using the Sheffield Alcohol Policy Model was used to quantify the expected benefit of introducing a minimum price of 50 pence per unit, reporting an expected fall in alcohol-related deaths by 60 in the first year and a financial saving from harm reduction of £942 million over 10 years.[18 19] Nalmefene is currently reimbursed without restriction in the UK in Scotland and in Wales for its approved indication.[20 21] Nalmefene has also received a preliminary recommendation from the NICE Appraisal Committee within its marketing authorisation and without restriction.[22] The final NICE guidance will be published in November 2014.[23]

This article reports on a Markov model that evaluated, as a primary objective, whether nalmefene used in combination with psychosocial support was cost-effective compared with psychosocial support alone in alcohol-dependent patients with a high/very high DRL, in line with the indication for nalmefene.[11] The perspective was that of the National Health Service (NHS) in England and Wales. As a secondary objective, to evaluate the public health benefit of patients entering treatment for alcohol dependence, this model assessed the avoidance of alcohol-attributable diseases, injuries and deaths with nalmefene plus psychosocial support versus psychosocial support alone and versus a 'no treatment' arm of continuous high-risk drinking patients.

METHODS

Overview

We developed a Markov model to estimate the direct medical costs and changes in quality-adjusted life years (QALYs) attributable to alcohol treatment and alcohol-attributable harmful events from the perspective

Table 1 Categorical levels for average volume of pure alcohol per day for women and men[16]

Category	Average volume of pure alcohol per day for women (g)	Average volume of pure alcohol per day for men (g)
WHO-criteria for risk of consumption on a single drinking day in relation to acute problems		
Low risk	0–20	0–40
Medium risk	21–40	41–60
High risk	41–60	61–100
Very high risk	>61	>101
WHO-criteria for risk of consumption on a single drinking day in relation to chronic harm		
I (low risk)	0–20	0–40
II (medium risk)	21–40	41–60
III (high risk)	≥41	≥61

of the NHS in England and Wales. A secondary aim was to assess the public health benefit of treatment for alcohol dependence in terms of the number of alcohol-attributable events avoided. The economic analysis was conducted in Microsoft Excel 2010. A Markov model was considered appropriate for modelling the effects of reducing alcohol consumption, since the natural history of the condition could be described as discrete health states, defined based on DRLs (table 1). The 5-year time horizon of the model was divided into two phases: a short-term phase lasting 1 year and a subsequent long-term phase spanning years 2–5. We evaluated the primary health effects of treatment using efficacy data from the three nalmefene clinical trials to inform the level of reduction of alcohol consumption in alcohol-dependent patients for the first year.[14 15] Patient-level data from the three nalmefene trials were pooled and computed for their inclusion in the model using the statistical software SAS V.9.2. The clinical effect for the short-term phase closely modelled the drinking patterns observed in the clinical trials, while drinking patterns for the long-term phase were derived by extrapolating results from these trials. We calculated the secondary effects of treatment on alcohol-attributable harmful events using evidence derived from the published literature.

The model had two intervention arms for the cost-effectiveness assessment: nalmefene plus psychosocial support and psychosocial support alone. Psychosocial support was considered the most appropriate comparator for nalmefene since NICE guidelines recommend that psychosocial intervention is the preferred treatment option in alcohol-dependent patients for whom reduction of alcohol consumption is a medically relevant treatment approach, but who do not require immediate detoxification.[8] In addition, clinical data for the use of naltrexone and acamprosate in these patients are limited, therefore NICE recommends these treatments only for patients who fail psychosocial intervention alone.[8] In the cost-effectiveness analysis, we reported treatment effect with nalmefene plus psychosocial support versus psychosocial support alone in terms of QALYs, a common health measure capturing changes in morbidity and mortality.

A third arm of continuous high-risk drinkers was included as a 'no treatment' arm for an additional exploratory analysis to assess the public health benefit of reducing the number of alcohol-attributable harmful events on entering treatment for alcohol dependence. These were patients deemed eligible for treatment with nalmefene, having high or very high DRLs at baseline and randomisation. This arm extended the distribution of patients across DRLs recorded in the prebaseline period of the nalmefene clinical trials over the model time horizon.

Patient population

The model population was based on a subsample of patients from the three nalmefene clinical trials: patients who continued to have a high/very high DRL during the 2-week period between baseline and randomisation (table 2). These patients represent the population that benefits most from treatment with nalmefene, and thus constitute the licensed population for nalmefene.[11]

Treatment efficacy

Treatment efficacy was modelled primarily by changes in the level of alcohol consumption, reflected as differences between treatment arms in the probabilities of transitioning between DRL health states. We modelled the efficacy of nalmefene plus psychosocial support versus psychosocial support alone using data from the three nalmefene clinical trials: ESENSE 1 and ESENSE 2 assessed treatment efficacy for 6 months,[14] while the SENSE study assessed efficacy for 1 year.[15] All three trials compared nalmefene plus BRENDA versus placebo plus BRENDA. The BRENDA approach is a form of psychosocial support provided by clinicians to manage chronic behavioural problems in primary and specialist care and was developed specifically for use with medication to promote adherence to treatment.[24]

Key efficacy end points in all three studies were the reduction in number of HDDs per month and daily TAC. Pooled data from these trials were used in our model (table 3). We used the nalmefene plus BRENDA

Table 2 Patient population characteristics from ESENSE 1, ESENSE 2 and SENSE trials (high/very high DRL at baseline and randomisation)[14 15]

Characteristic	Pooled estimates
Age (mean years)	48
Gender (% men)	69
DRL (%)	
Very high risk	58
High risk	42

DRL, Drinking risk level.

Table 3 Adjusted change from baseline in monthly HDDs and TAC (FAS, OC, MMRM)—ESENSE 1, ESENSE 2 and SENSE (high/very high DRL at baseline and randomisation)[14 15]

	Number of participants at baseline					
	Nalmefene +PS	Placebo +PS	End point	Mean difference to placebo in the change from baseline	95% CI	p Value
Pooled studies (month 6) (ESENSE 1 and 2, SENSE)	460	364	HDD	−3.01 days/month	−4.36 to −1.66	<0.0001
			TAC	−14.22 g/day	−19.96 to −8.47	<0.0001
SENSE (month 13)	141	42	HDD	−3.60 HDDs/month	−6.52 to −0.67	0.0164
			TAC	−17.31 g/day	−30.87 to −3.76	0.0129

DRL, drinking risk level; FAS, full analysis set; HDD, heavy drinking day; MMRM, mixed model repeated measures; OC, cbserved cases; PS, psychosocial support; TAC, total alcohol consumption.

arms from the trials to model the nalmefene plus psychosocial support cohort, and the placebo plus BRENDA arms to model the psychosocial support cohort. Pooled data from the three trials have been used to derive monthly transition probabilities between the drinking level health states in the first year of the model, as well as treatment discontinuation. Data from SENSE were used to inform transition probabilities in the long-term phase of the model (years 2–5).

The third 'no treatment' arm of continuous high-risk drinkers was modelled using the monthly prebaseline distributions and drinking characteristics of nalmefene's licensed population from the nalmefene clinical trials, reproduced for the whole model time horizon. TAC and HDDs taken from the monthly prebaseline period were used to represent the drinking level and pattern for these patients each month in the model. For the 'no treatment' population, the mean number of HDDs was 21.8 and the mean daily TAC was 104 g/day for each month (table 4).

As a secondary measure, efficacy was further assessed by modelling the secondary effects of alcohol consumption on the incidence of alcohol-attributable harmful events.

Model structure

We applied a 1-month cycle length in the model's within-trial short-term phase (year 1), as aligned with the duration of patient follow-up in the nalmefene clinical trials and the recommended frequency of follow-up with a clinician in the summary of product characteristics for nalmefene.[14 15 25] During the short-term phase, we modelled five key health states in line with DRL categories as defined by the WHO[16]: very high, high, medium and low risk of drinking and abstinence (figure 1 and table 1). In the long-term phase (years 2–5), we set the cycle length to 1 year based on the availability of reliable clinical data particularly with regard to the maintenance of effect and probability of relapse to heavy drinking. A long cycle length necessitating fewer cycles in the long-term phase also limited the uncertainty from extrapolating outcomes from the nalmefene clinical trials beyond the duration of the trials. The clinical data informed the three health states used for the long-term phase of the model (years 2–5): controlled drinking (including low DRL and abstinence), medium risk drinking, and high or very high-risk drinking (figure 1).

Throughout the 5-year time horizon, in addition to the drinking level health states, we included health states for serious and temporary alcohol-attributable diseases and injuries. These represent alcohol-attributable diseases and injuries known to incur a significant cost to the healthcare system, that had strong evidence for their association with alcohol consumption, and that occurred during the 5-year time horizon of the model. We also included a death state. Temporary harmful events were modelled as a tunnel state lasting 1 month, while serious harmful events involved the patient moving to a permanent postevent state outside of the drinking health states. The use of a 5-year time horizon was considered an appropriate time to capture relevant costs and effects pertaining to the treatments being compared without reaching unacceptable uncertainty in terms of patients' long-term drinking behaviour, treatment needs and development of chronic diseases from long-term alcohol consumption.

Patients entered the short-term phase of the model at either high or very high DRL. At each cycle patients had the chance of transitioning between any of the five short-term DRL states, or remaining in the health state they were currently in (figure 1). At the end of the short-term phase, patients in the low DRL state or abstinent after responding to treatment transitioned to the controlled drinking health state where they did not receive further treatment (figure 1). This is aligned with the fact that clinical data for the use of nalmefene under randomised controlled conditions are available for a period of 12 months, and that caution is advised in the drug license if nalmefene is prescribed for more than 1 year.[25] We considered patients in the medium DRL state after the first 12 months to have partially responded to treatment. We assumed that these patients would continue in the same treatment arm in the long-term medium DRL state, given the risks of acute and chronic harms at this level of drinking. Patients in this state had the possibility of transitioning each cycle to either the long-term high/very high DRL state or the

Table 4 Proportion of patients starting in each health state, nalmefene intake and alcohol consumption parameters associated with the short-term and long-term DRL health states[14 15]

Item	Initial proportion of patients at model start (%)	Mean alcohol consumption (g/day)	Mean alcohol consumption per HDD (g/day)	Mean number of HDDs per month	Mean nalmefene intake per month*
Short-term DRL health states					
Males					
Very high risk	42	134	153	25	20.5
High risk	58	78	113	19	19.9
Medium risk	0	50	107	10	16.5
Low risk	0	21	81	3	13.9
Abstinence	0	–	–	–	8.8
Females					
Very high risk	42	94	108	24	19.1
High risk	58	50	74	19	18.9
Medium risk	0	29	67	9	16.5
Low risk	0	11	50	3	14.8
Abstinence	0	–	–	–	7.7
Long-term DRL health states					
Males					
Very high and high risk	–	104	132	22	NA
Medium risk	–	50	107	10	16.5
Controlled drinking	–	16	65	3	NA
Females					
Very high and high risk	–	75	93	22	NA
Medium risk	–	29	67	9	16.5
Controlled drinking	–	9	40	2	NA

Mean estimates or counts of patients based on observed case data from ESENSE 1, ESENSE 2 and SENSE were pooled for the first 6 months to inform the model DRL health state transition probabilities and utility values for the DRL health states. Following the first 6 months, data from SENSE were used up to 12 months, after which data from this study were extrapolated to the 5-year model time horizon.
*Pooling the three nalmefene trials, nalmefene intake was 35% of the days over one year when dividing the number of days of intake by the full study period; and it was 56% of the days over 1 year when dividing the number of days of intake per individual patient by the number of days the patient was in the trial (until dropout or end of study).
DRL, drinking risk level; HDD, heavy drinking day.

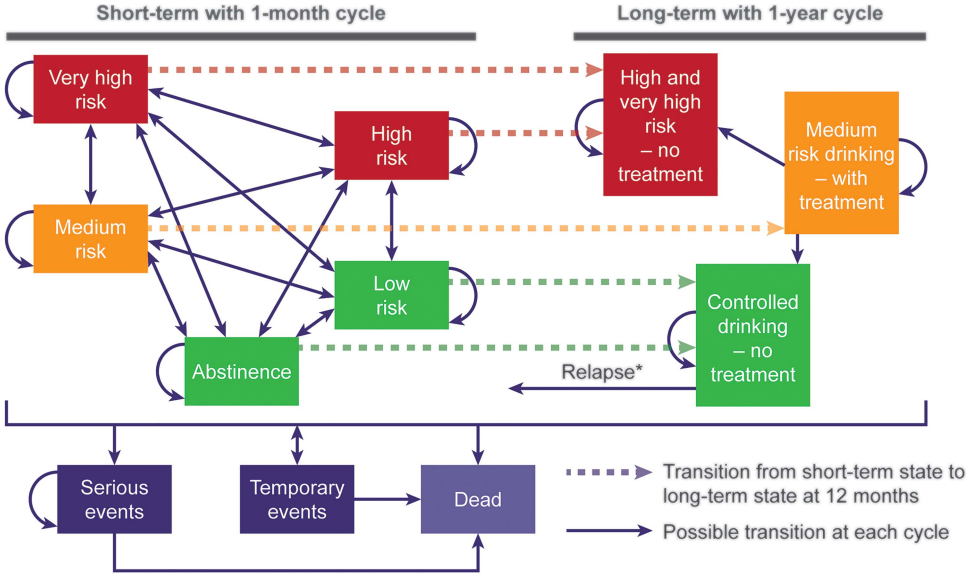

Figure 1 Summary of the health states and events incorporated in the short-term and long-term phases of the model. *At each cycle, patients in the controlled drinking state could relapse into the drinking state they were in at the start of the model (high drinking risk levels (DRL) or very high DRL states in the short-term phase of the model), and hence to the original treatment they were successful with.

controlled drinking state, or staying in the medium DRL state (figure 1). We considered patients in the high and very high DRL states at the end of the first 12 months as having not responded to treatment. These patients therefore transitioned to the long-term high/very high DRL state without receiving further treatment and were modelled as continuous drinkers for the remainder of the model's time horizon. It was a conservative assumption to suppose that patients would not begin alternative treatment.

Each year, patients in the controlled drinking state of the long-term phase could relapse into their original drinking state (high or very high DRL) in the short-term phase of the model, receiving a second round of treatment using the strategy that was initially successful at controlling their alcohol consumption; this was considered a clinically relevant supposition. Patients who relapsed returned to the beginning of the model's short-term phase, both in terms of DRL and state transition probabilities. Patients not experiencing a relapse remained in the controlled drinking state for the remainder of the model's time horizon (figure 1).

Throughout the model time horizon, at each cycle all patients had a chance of experiencing a harmful event, including death, at rates specific to each health state. Patients could move from any of the health states to the death state, either due to alcohol-attributable harmful events or all-cause mortality (figure 1).

As seen during clinical trials for nalmefene, dropouts from treatment could occur from nalmefene-related adverse events (mainly nausea, headache, dizziness or insomnia) or due to other reasons (mainly withdrawal of consent or protocol violation).[14 15] After dropping out due to a nalmefene-related adverse event, patients stayed in the nalmefene plus psychosocial support cohort but were subject to transition probabilities from the psychosocial support alone arm. We assumed that these patients would be willing to continue receiving psychosocial support, but not nalmefene due to excessive discomfort from the adverse events. Patients in either treatment arm dropping out for reasons other than adverse events transitioned to a 'continuous high risk drinking' state, where they remained permanently at a high or very high DRL. This was deemed to be a conservative assumption related to treatment failure.

Model parameters

Four categories of parameters were included in the model: (1) health state transition probabilities for DRLs, based on the three nalmefene clinical trials for the short-term phase of the model, and based on extrapolation from the nalmefene trials and from complementary sources and assumptions for the long-term phase; (2) incidence of alcohol-attributable diseases, injuries and deaths based on published epidemiological risk-relation studies; (3) utilities taken from the nalmefene clinical trials for drinking health states for the base-case, from a UK naturalistic study for the sensitivity analysis, and from UK published sources for alcohol-attributable diseases and injuries; and (4) resource use and costs related to alcohol-dependence treatment based on the nalmefene clinical trials, and on UK sources for the treatment of alcohol-attributable diseases and injuries.

Health state transition probabilities for DRLs

The initial proportions of patients in the high and very high DRL health states at the start of the model and the monthly probabilities of transitioning between the five health states in the short-term phase of the model (including treatment dropout) were calculated as the pooled proportions at randomisation and in each health state each month, respectively, in the nalmefene clinical trials. The monthly transition probabilities were based on the count of patients (observed cases) each month for compared treatment cohorts (table 4; see online supplementary table A).

For the long-term phase of the model, we derived the yearly health state transition probabilities for patients in the medium DRL health state using the average transition probabilities of medium DRL patients in the last 6 months of the longer-term SENSE trial (see online supplementary table B). This was judged an appropriate approach, with the model conclusion subsequently found to be insensitive to these data because of the small incremental proportion of patients between treatments at medium DRL at 12 months (table 8).

To model relapse from the long-term controlled drinking state, we used a similar approach to Barbosa *et al*,[26] with the probability of relapse based on the rates of patients relapsing from treatment or retaining the same drinking state in a 10-year study performed by Taylor *et al*.[27] In Taylor *et al* the yearly recurrence to heavy drinking after response was estimated to be 14–19%; in the current model, we conservatively used 19%.

Incidence of alcohol-attributable diseases, injuries and death

Alcohol-attributable events considered in the model were categorised based on their pathophysiology of occurrence with regard to level and pattern of alcohol consumption (table 5). We implemented these in the model using risk equations that were developed by the Canadian Centre for Addiction and Mental Health (CAMH) using published meta-analyses based on systematic literature reviews and were previously used for a population-based analysis.[28]

The likelihood of each patient experiencing a harmful event depended on the level and pattern of alcohol consumption. The risk of patients experiencing alcohol-attributable harmful events (both morbidity and mortality) was calculated as shown in equation 1, where Population Risk Event(i) is the risk of an event i for a given time period for the general population (see online data supplementary table C), and RREvent(i)(x) is the relative risk of having event i given alcohol consumption of x, as derived from the CAMH risk equations.

Table 5 Alcohol-attributable harmful events included in the model

Type	Event	Effect	Modelled as
Continuous-drinking events			
Alcohol-attributable diseases associated with continuous alcohol consumption over time	Lower respiratory infections	Temporary	Tunnel state*
	Haemorrhagic stroke	Serious	Postevent state†
	Cirrhosis of the liver	Serious	Postevent state
	Pancreatitis	Serious	Postevent state
Immediate-drinking events			
Alcohol-attributable diseases or injuries incurred from a single episode of heavy alcohol consumption	Ischaemic heart disease	Serious	Postevent state
	Ischaemic stroke	Serious	Postevent state
	Transport injuries	Temporary	Tunnel state
	Injuries other than from transport	Temporary	Tunnel state

*1 month.
†Serious event state; patients could also transition to the death absorbing state from a temporary event, serious event or from general mortality.

Equation 1 Risk of experiencing alcohol-attributable harmful events

$$\text{Personal Risk Event}(i,x) = \text{Population Risk Event}(i) \times \text{RREvent}(i)(x) \quad (1)$$

We calculated the Personal Risk Event(i,x) in accordance with the level of alcohol consumption. To consider both the level and pattern of consumption, we used pooled alcohol consumption data from the ESENSE 1, ESENSE 2 and SENSE trials to derive mean levels of alcohol consumption per day, per HDD and the mean number of HDDs per month for each DRL (table 4). Depending on the event's pathophysiology of occurrence, the Personal Risk Event(i,x) of experiencing it depended on either immediate or continuous drinking level. For events associated with immediate drinking, the Personal Risk Event(i,x) was determined using the daily drinking level per HDD and the number of HDDs per month. Thus, on non-HDDs, the Personal Risk Event(i,x) was the same as the risk of the event occurring in the general population. For harmful events as a result of continuous drinking, we based the Personal Risk Event (i,x) of experiencing these on average monthly drinking levels. The resulting relative risks and probabilities used in the model are presented in online supplementary tables D–G.

In line with earlier publications, we did not deem it realistic to assume that a patient would experience a higher risk of transport-related or other injuries for the entire day.[2 29] To account for this we set the time that the patient was at risk of experiencing these events to 3 h. This assumption was developed by Taylor *et al*, who took into account the number of drinks consumed, the rapidity of consumption, the rate of liver metabolism and the time taken to reach a certain blood alcohol concentration to identify 3 h as a general assumption for the time after consuming alcohol during which there is a significantly higher risk of harmful events.[30]

Utilities

We incorporated utility weights for all drinking health states and alcohol-attributable harmful events in the model (table 6). In the three nalmefene clinical trials, quality of life was measured using EQ-5D at baseline, 3 and 6 months, and additionally at 12 months for SENSE. For health state utilities in the base-case, we estimated the mean utility difference between the two treatment strategies in the short-term phase of the model using the area between the curves of pooled adjusted mean utility scores for nalmefene and placebo patients from the trials at every 3 months from baseline to 1 year (adjusted for the baseline utility and assuming a linear transition between the mean utilities at each time point). This method of applying utilities from a clinical trial was informed by the NICE Clinical Guideline on alcohol use disorders and has the advantage of being able to capture the disutility of adverse events relating to nalmefene.[31] For the long-term phase of the model, we derived utility weights for each of the three DRL states from pooled data from the nalmefene trials (table 6). Utility weights for drinking health states were subsequently varied in a sensitivity analysis.

During the short-term phase of the model, for both temporary and serious harmful events, patients incurred event-related utility decrements (and the addition of event-related costs) applied to the utilities (and costs) incurred independently by their DRL health states (table 6). Using the same approach as for the Sheffield Alcohol Policy Model,[19] disutilities were calculated using the utilities of harmful events proposed in the Sheffield Alcohol Policy Model (table 6),[19] subtracted from the general population utility (0.852). In the long-term phase of the model, for temporary and serious harmful event states, the QALYs (and costs) related to the event itself were calculated for the patient, using the utility value from the Sheffield Alcohol Policy Model and calculating a QALY for the time the patient was in that health state. For temporary events, accumulation of QALYs from the drinking state was considered, whereas

Table 6 Costs, utilities and resource use inputs to the model for the base-case analysis

Base-case

Parameter DRL health states	Values Utility	Source
Short-term DRLs	0.017*	ESENSE 1, ESENSE 2, SENSE[14 15]
Long-term high/very high DRL	0.795	ESENSE 1, ESENSE 2, SENSE[14 15]
Long-term medium DRL	0.825	ESENSE 1, ESENSE 2, SENSE[14 15]
Long-term controlled drinking	0.862	ESENSE 1, ESENSE 2, SENSE[14 15]

Treatment	Proportion of visits	Number of visits in first month	Number of subsequent visits per month	Cost	Source
Nalmefene, one dose	–	–	–	£3.03	MIMS[36]
Visit to GP including psychosocial support†	75%	3	1	£53	PSSRU[34]
First attendance to specialised care including psychosocial support	25%	3	1	£222	PSSRU[34]
Follow-up attendance to specialised care including psychosocial support		3	1	£98	PSSRU[34]

Alcohol-attributable harmful events‡	Utility	Source	Cost per event	Source
Ischaemic heart disease	0.643	Sheffield Alcohol Policy Model[19]	£2407	Sheffield Alcohol Policy Model§[19]
Ischaemic stroke	0.564	Sheffield Alcohol Policy Model[19]	£3949	Sheffield Alcohol Policy Model§[19]
Haemorrhagic stroke	0.657	Sheffield Alcohol Policy Model[19]	£5602	Sheffield Alcohol Policy Model§[19]
Cirrhosis of the liver	0.494	Sheffield Alcohol Policy Model[19]	£3623	Sheffield Alcohol Policy Model§[19]
Pancreatitis	0.447	Sheffield Alcohol Policy Model[19]	£4224	Sheffield Alcohol Policy Model§[19]
Lower respiratory infections	0.200¶	Sisk *et al*[37]	£2999**	NHS reference cost database (2010–2011)[33]
Motor vehicle accidents	0.598	Sheffield Alcohol Policy Model[19]	£5283	Sheffield Alcohol Policy Model§[19]
Injuries other than from transport	0.592††	Sheffield Alcohol Policy Model[19]	£5116	Sheffield Alcohol Policy Model§[19]

*QALY difference between nalmefene plus psychosocial support and psychosocial support alone for the first year of treatment, calculated from the clinical trials ('area between the curves'). QALYs lost were later applied to each arm for the consideration of alcohol-attributable harmful events. A mixed model repeated measures analysis was carried out using EQ-5D utilities and observed case data from all three trials to estimate treatment effect for the first 6 months. The model used an unstructured covariance matrix and included country, sex, time (months 1–6) and treatment as fixed effects, as well as baseline value-by-time and treatment-by-time interactions.
†An estimate based on a 17.2 min visit to a general practitioner.
‡Hospital admission data only took into account the first diagnosis for hospitalisation and not the multiple alcohol-attributable conditions that are often diagnosed and managed during the same hospitalisation.
§Based on ICD-10 code of events, including the following components associated with one hospital admission: inpatient visits, outpatient visits, accident and emergency visits, ambulance general practitioner consultation, nurse visits and other healthcare costs. For events with multiple codes, the weighted average calculated from the proportion of admissions reported in the Hospital Episode Statistics (2010–2011) for England was used.
¶The utility score from Sisk *et al*[37] was during patient hospitalisation. Thus it was applied to the model for 9 days, which was the weighted average length of hospital stay for lower respiratory infections.[33]
**Weighted average using Elective Inpatient HRG Data; currency code DZ11A, DZ11B, DZ11C, DZ23A, DZ23B, DZ23C.
††The utility value used in the model for other injuries was calculated as a weighted average combining the utility scores presented in the 'Sheffield alcohol policy model' for the subevents included in 'other injuries' (based on International Classification of Disease-10 codes) and these were matched with the number of admissions reported in Hospital Episode Statistics (2010–2011) for England (ICD-10 data used for modelling the incidence of alcohol-attributable events).[19]
Source: The utilities used in the Sheffield alcohol policy model were derived from a single source, the Health Outcomes Data Repository (HODaR) 2008, to avoid potential bias and variability between studies.[38] The HODaR data measure utilities using the EQ-5D as recommended by NICE for health economic evaluations. Data used in the Sheffield alcohol policy model were collected by the Cardiff & Vale NHS Hospital Trust serving a local population of 424 000 and providing tertiary care for the whole of Wales. Patients discharged from hospital were requested to complete an EQ-5D questionnaire 6 weeks after their discharge. Data were collected on: demography, health utility (EQ-5D index) and diagnoses (ICD-10). A mean utility value was extracted for each condition based on diagnoses (or ICD-10 codes) and adjusted for age using the % increment/decrement observed for utilities in the general population.
DRL, drinking-risk level; GP, general practitioner; NHS, National Health Service; No., number; QALY, quality-adjusted life year.

for serious events the event QALY was applied without considering QALYs associated with drinking alcohol.

Resource use and costs

Costs and resource use included in the model were direct medical costs for the treatment of alcohol dependence and for the management of alcohol-attributable harmful events (table 6). The costs for treating alcohol dependence included the cost of the drug and the cost of 20 min sessions of psychosocial support, the latter of which was assumed to be provided during medical consultations at both general and specialist practices (table 6). This is aligned with experience in the nalmefene clinical trials and current practice in the UK.[11 32] Nalmefene intake per DRL was calculated by pooling data from the three clinical trials (table 4). In these trials, nalmefene posology was as-needed, in line with its indication.[25] We did not include costs for adverse events associated with nalmefene use in the model, as the common adverse events reported in the three clinical trials were mild (nausea, headache, dizziness and insomnia) from a clinical perspective and were not thought to incur significant additional costs.[14 15] Costs and resource use associated with the occurrence of alcohol-attributable harmful events were based on those used in the Sheffield Alcohol Policy model with the exception of lower respiratory infections, which were calculated using the NHS reference cost database (table 6).[19 33]

We inflated costs to 2010/2011 when relevant, using the Hospital and Community Health Services Index.[34] In addition, we discounted all costs and outcomes in the model at an annual rate of 3.5%, in line with NICE recommendations.[35]

Sensitivity analysis

We conducted probabilistic sensitivity analysis (PSA) for 5000 iterations for all parameters in the model estimated with uncertainty (see online supplementary table H), using Monte Carlo simulation in Microsoft Excel 2010.[39] Parameter uncertainty was defined by probability distributions as recommended by Briggs *et al*.[40] Depending on the model parameter, we based uncertainty around the parameter estimates on calculated or reported patient counts, SEs or range. β and Dirichlet distributions were used for transition probabilities and utility weights, γ distributions for costs and normal distributions for the regression parameters used in calculating the relative risks of alcohol-attributable harmful events. The distributions used in the PSA for each parameter are given in online supplementary table H.

We performed one-way sensitivity analyses (OSA) on 128 parameters to investigate each individual parameter's impact on the cost-effectiveness of nalmefene (see online supplementary table H). These corresponded to all model parameters except the transition probabilities between drinking levels and dropout rates, which we investigated in the PSA. Using an approach recommended by Briggs *et al*,[41] we based the ranges tested in the OSA on the statistical uncertainty around the estimates using their 95% CI. When a 95% CI was not available for a parameter, we defined a credible range. For parameters close to the population data, a range was defined as the 95% CI assuming that the SE was 10% of the mean value, and for parameters based on population sample data the 95% CI assuming a SE of 20% of the mean value was used. For other parameters where statistical uncertainty was not available, we varied estimates by range of interest within credible values informed by clinical practice. A list of the parameters varied in the sensitivity analyses is given in online supplementary table H.

Table 7 Utility values from the STREAM study used in scenario sensitivity analyses

DRL health states (entire time horizon)	Utility	Source
Very high risk	0.531	STREAM[42]
High risk	0.609	STREAM[42]
Medium risk	0.714	STREAM[42]
Low risk	0.755	STREAM[42]
Abstinence	0.816	STREAM[42]

DRL, drinking risk level.

Additionally, we ran the model under a number of alternative scenarios to investigate the impact of varying: the time horizon in the model from 5 years through to 1 year; the nalmefene intake from as-needed to every day; and utility weights for DRL health states using EQ-5D data from a naturalistic disease management study of patients with alcohol dependence in the UK primary care setting at the general practitioner level (STREAM study) (table 7).[42] We also included scenarios to assess the effect of removing all harmful events from the model.

Quality-control procedures were performed on the final version of the cost-effectiveness model and included verification of all input data with the original sources, a series of diagnostic tests to confirm that the model had correctly applied all formulae, and a review of the model calculations and programming.[43]

RESULTS

Patient evolution through the 5-year time horizon

During the first year of the model, the use of nalmefene plus psychosocial support considerably reduced the number of patients in the high and very high DRLs compared with psychosocial support alone, and increased the number of patients in the low and abstinent DRLs. These observations are in favour of nalmefene plus psychosocial support compared to psychosocial support alone, and are aligned with results from the clinical trials (table 8). After 1 year, these trends continued for the compared treatment arms. This incremental difference in treatment efficacy over the model time horizon can be seen in terms of the resulting additional alcohol-attributable events in the psychosocial support arm (table 8).

Table 8 Proportions of patients per health state at the end of each year

	Very high risk	High risk	Medium risk	Low risk	Abstinence	Death*	Serious events†
Year 1							
NMF	0.18	0.17	0.12	0.40	0.10	0.01	0.02
PS	0.26	0.27	0.14	0.22	0.08	0.01	0.02
	Very high risk/high risk		Medium risk	Low risk/abstinence (controlled drinking state)		Death*	Serious events†
Year 2							
NMF	0.38		0.07	0.50		0.01	0.04
PS	0.56		0.07	0.30		0.02	0.04
Year 3							
NMF	0.40		0.04	0.47		0.02	0.06
PS	0.58		0.05	0.28		0.02	0.07
Year 4							
NMF	0.42		0.03	0.44		0.03	0.07
PS	0.60		0.03	0.25		0.03	0.09
Year 5							
NMF	0.44		0.03	0.40		0.04	0.09
PS	0.60		0.02	0.22		0.04	0.11

*Absorbing state.
†Serious event state ('post-event state'): Ischaemic heart disease; Haemorrhagic stroke; Ischaemic stroke; Cirrhosis of the liver; Pancreatitis.
NMF, nalmefene plus psychosocial support; PS, psychosocial support alone.

Incidence of alcohol-attributable harmful events

Nalmefene plus psychosocial support led to fewer harmful morbidity and mortality events than psychosocial support alone (table 9), which is in line with the differences in drinking behaviours observed in the two arms. After 5 years, nalmefene plus psychosocial support led to the avoidance of 7179 (95% CI 4244 to 12 654) alcohol-attributable diseases or injuries and 309 (95% CI 181 to 641) deaths per 100 000 patients versus psychosocial support alone. The exploratory analysis modelling the 'no treatment' arm demonstrated the important public health benefit for patients entering treatment for alcohol dependence: compared with 'no treatment', nalmefene plus psychosocial support led to the avoidance of 20 202 (95% CI 13 942 to 27 243) alcohol-attributable diseases or injuries and 864 (95% CI 558 to 1469) deaths per 100 000 patients.

The differences in the incidence of alcohol-attributable diseases or injuries between the model arms resulted in cost savings for the English healthcare system with nalmefene use after 1 and 5 years of treatment initiation (table 10).

Base-case analysis

Taking into consideration the outcomes and costs generated by the model at the end of the 5-year time horizon, the base-case analysis concluded that nalmefene in combination with psychosocial support had an incremental cost-effectiveness ratio (ICER) of £5204 per QALY gained compared with psychosocial support alone (table 11). Thus, adding nalmefene to psychosocial support is expected to be a cost-effective option at a £20 000 per QALY gained decision threshold, compared with psychosocial support alone.

The clinical improvement seen with nalmefene plus psychosocial support compared with psychosocial support alone was reflected in the larger gain of QALYs with nalmefene plus psychosocial support than with psychosocial support alone (table 11). An analysis of the costs associated with the two treatment strategies revealed that the largest proportion of the costs for both strategies was for medical visits followed by costs due to harmful events (table 11).

Probabilistic sensitivity analysis

The PSA estimated that there is 94% probability that nalmefene plus psychosocial support is cost-effective at a willingness-to-pay threshold of £20 000 per QALY gained compared to psychosocial support alone (figure 2).

Results of the one-way sensitivity analysis

Overall, the analysis concluded that the base-case results were robust. The parameters with the greatest impact on the cost-effectiveness results were increasing the number of medical visits per month (independently, for both treatments) from one to two visits per month, and the utility values used for the short-term phase (figure 3). Of all 128 parameters examined in the OSA, the results of the analysis for the parameters identified as having the greatest impact on cost-effectiveness are presented in online supplementary table I. No OSAs altered the conclusion of the base-case analysis that adding nalmefene to psychosocial support is a cost-effective opportunity for healthcare systems in the UK.

Results of the scenario analysis

DRL health state utility values

A scenario analysis using the DRL health state utility values from the STREAM study resulted in a decrease in the cost

Table 9 Number of patients experiencing modelled harmful events at one year and five years per 100 000 patients for nalmefene plus psychosocial support, psychosocial support alone or patients in the 'no treatment' arm

Event per 100 000 patients (95% CI)	1 year			Difference		5 years			Difference	
	NMF	PS	No Tx	PS-NMF	No Tx-NMF	NMF	PS	No Tx	PS-NMF	No Tx-NMF
Ischaemic heart disease	1186 (861 to 1732)	1303 (901 to 1995)	1573 (991 to 2526)	117 (39 to 271)	387 (129 to 802)	5834 (4339 to 8526)	6494 (4540 to 9979)	7686 (4841 to 12 202)	660 (200 to 1678)	1852 (528 to 3765)
Ischaemic stroke	269 (199 to 393)	297 (209 to 454)	359 (232 to 580)	28 (9 to 63)	90 (32 to 188)	1348 (998 to 1973)	1514 (1053 to 2361)	1805 (1123 to 2901)	167 (54 to 439)	457 (132 to 959)
Haemorrhagic stroke	105 (90 to 127)	114 (95 to 142)	136 (107 to 179)	9 (4 to 17)	31 (16 to 52)	427 (368 to 534)	477 (401 to 624)	571 (447 to 750)	50 (25 to 99)	143 (75 to 222)
Liver cirrhosis	203 (150 to 287)	244 (175 to 364)	352 (234 to 533)	41 (22 to 83)	148 (83 to 250)	885 (697 to 1260)	1092 (851 to 1623)	1500 (1093 to 2171)	207 (114 to 407)	615 (368 to 932)
Pancreatitis	229 (156 to 365)	288 (190 to 486)	451 (274 to 766)	59 (28 to 130)	222 (115 to 408)	778 (610 to 1169)	960 (735 to 1524)	1358 (961 to 2135)	182 (91 to 394)	580 (336 to 986)
Lower respiratory tract infections	918 (687 to 700)	968 (689 to 706)	1109 (713 to 732)	50 (−3 to 10)	192 (23 to 34)	2917 (2627 to 2903)	3256 (2882 to 3266)	3843 (3319 to 3551)	339 (135 to 496)	926 (543 to 809)
Transport injuries	548 (524 to 590)	720 (681 to 778)	1109 (1097 to 1119)	172 (124 to 224)	560 (518 to 584)	2515 (2333 to 2980)	3505 (3248 to 4166)	5318 (5070 to 5488)	990 (619 to 1513)	2803 (2309 to 2979)
Injuries other than transport	3091 (1870 to 5174)	3911 (2336 to 6566)	5734 (3339 to 9596)	820 (418 to 1486)	2643 (1457 to 4460)	13 657(9089 to 22 419)	18 241 (12 125 to 30 474)	26 483 (16 680 to 41 824)	4584 (2411 to 9126)	12 826 (7107 to 20 140)
Deaths from serious events	260 (200 to 442)	348 (255 to 621)	493 (332 to 939)	88 (52 to 192)	233 (131 to 503)	1273 (1021 to 2013)	1491 (1171 to 2461)	1892 (1393 to 3216)	219 (117 to 518)	620 (348 to 1226)
Deaths from short-term events	185 (170 to 215)	225 (203 to 266)	270 (237 to 324)	41 (29 to 53)	86 (65 to 110)	1013 (931 to 1149)	1103 (1010 to 1279)	1257 (1122 to 1458)	90 (51 to 162)	245 (161 to 339)
Total number of events	6549 (5074 to 8524)	7845 (5962 to 10 381)	10 823(7962 to 14 489)	1296 (788 to 2004)	4273 (2842 to 5950)	28 361 (23 817 to 38 177)	35 540 (29 699 to 49 069)	48 563 (38 527 to 64 212)	7179 (4244 to 12 654)	20 202 (13 942 to 27 243)
Total number of deaths	445 (384 to 628)	573 (479 to 853)	763 (599 to 1212)	129 (87 to 235)	319 (212 to 585)	2285 (2021 to 3027)	2594 (2273 to 3595)	3149 (2634 to 4466)	309 (181 to 641)	864 (558 to 1469)

NMF, nalmefene plus psychosocial support; No Tx, 'No treatment' arm; PS, psychosocial support alone.

Table 10 Number and cost of alcohol-attributable harmful events avoided between the model arms

	One year		Five years	
	PS-NMF	No Tx-NMF	PS-NMF	No Tx-NMF
Difference in number of events per 100 000 patients (95% CI)	1296 (788 to 2004)	4273 (2842 to 5950)	7179 (4244 to 12 654)	20 202 (13 942 to 27 243)
Cost difference* per 100 000 patients (95% CI)	£5 900 000 (£3 200 000 to £10 100 000)	£19 300 000 (£11 600 000 to (£30 400 000)	£29 900 000 (£16 200 000 to £58 200 000)	£84 500 000 (£51 200 000 to £128 000 000)
Cost difference* per patient (95% CI)	£59 (£32 to £101)	£193 (£116 to £304)	£299 (£162 to £582)	£845 (£512 to £1280)

*Differences in costs are those incurred as a result of differences in harmful events only.
NMF, nalmefene plus psychosocial support; No Tx, 'No treatment' arm; PS, psychosocial support alone.

Table 11 Incremental cost, QALY, life year, cost per life year and cost per QALY for nalmefene plus psychosocial support versus psychosocial support alone (base-case results at 5 years)

Mean per patient (95% CI)	Nalmefene plus psychosocial support	Psychosocial support	Nalmefene plus psychosocial support vs psychosocial support
Total cost per patient	£2889 (£2557 to £3777)	£2454 (£2085 to £3436)	£434 (£197 to £675)
Medical visits for AD treatment (including psychosocial support)	£1187 (£1007 to £1822)	£1060 (£868 to £1567)	£127 (£43 to £359)
Cost of nalmefene drug treatment	£605 (£522 to £666)	n/a	£605 (£522 to £666)
Cost of harmful events	£1096 (£804 to £1657)	£1395 (£1009 to £2192)	−£299 (−£162 to −£582)
Life years per patient	4.42 (4.40 to 4.43)	4.41 (4.38 to 4.42)	0.01 (0.01 to 0.02)
QALYs per patient	3.57 (3.46 to 3.60)	3.48 (3.40 to 3.52)	0.08 (0.01 to 0.13)
Cost per life year	n/a	n/a	£49 174
Cost per QALY	n/a	n/a	£5204

All costs and outcomes in the model were discounted at an annual rate of 3.5%, in line with NICE recommendations,[35] and costs were inflated to 2010/2011 when relevant using the Hospital and Community Health Services Index.[34]
AD, alcohol dependence; QALYs, quality-adjusted life years.

per QALY gained to £1990 with 100% probability of cost-effectiveness at the £20 000 threshold (see online supplementary table J). This is expected, given the higher incremental variation between the DRL utility scores from this naturalistic study compared to those from the nalmefene clinical trials, where the patient inclusion and exclusion criteria pertaining to any randomised controlled trial would have reduced the variation in impact of interventions on patients' quality of life (table 6).

Time horizon

The model was sensitive to the time horizon, resulting in a cost per QALY gained of £24 412 and 35% probability of cost-effectiveness at the £20 000 threshold when a 1-year time horizon was used (see online supplementary table J). When considering the scenarios using 2-year, 3-year and 4-year time horizons, it becomes clear that the cumulative effect of incremental QALYs drives the improvement in cost-effectiveness results with increased time horizon (see online supplementary tables J and K). This incremental increase in QALY gain each year of the model time horizon is a result of the superior effectiveness for the nalmefene arm gained during the first 12 months. During this phase, patients in the nalmefene arm exhibited reduced alcohol consumption compared to those in the psychosocial support arm, thus when the long-term phase of the model began there was a higher proportion of patients in the controlled drinking state and a lower proportion of patients in the high/very high DRL health state for nalmefene plus psychosocial support than for psychosocial support alone. With the exception of the medium DRL health state (see online supplementary table B), no additional difference in treatment benefit between the arms was considered beyond the retained differences in proportions of patients in the different health states after the first 12 months. Although treatment-specific transition probabilities were used for the long-term medium DRL health state, the model results were insensitive to this feature when tested in an extreme scenario against nalmefene where all patients in the medium DRL health state at the end of 12 months transitioned to the high and very high DRL state if they were in the nalmefene arm, or to the controlled drinking state if they were in the comparator arm. An analysis using the STREAM utility values plus a 1-year time horizon proved cost-effective, showing an ICER of £13 364 with 89% probability of cost-effectiveness at the £20 000 threshold.

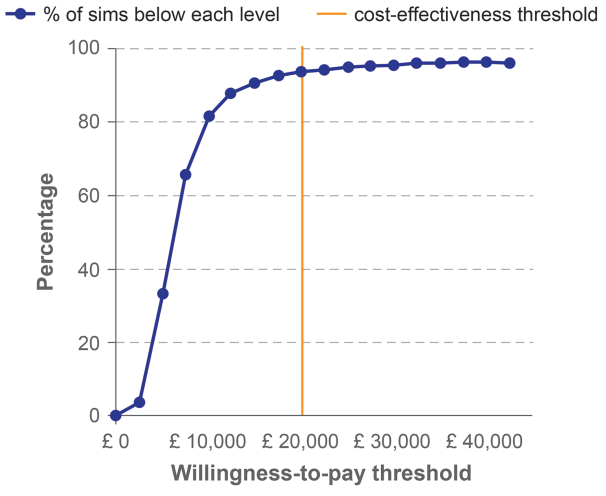

Figure 2 Cost-effectiveness acceptability curve for nalmefene plus psychosocial support versus psychosocial support alone (base-case results at 5 years). Sims: simulations.

Nalmefene intake

In the scenario investigating nalmefene intake, the use of nalmefene daily as opposed to on an as-needed basis resulted in a cost per QALY of £10 080 with 84% probability of being cost-effective at the £20 000 threshold. It should be noted that this scenario is not representative of real-life patterns of nalmefene intake, where nalmefene dose correlated with the level of alcohol consumption, as observed in the nalmefene clinical trials (table 5).[14]

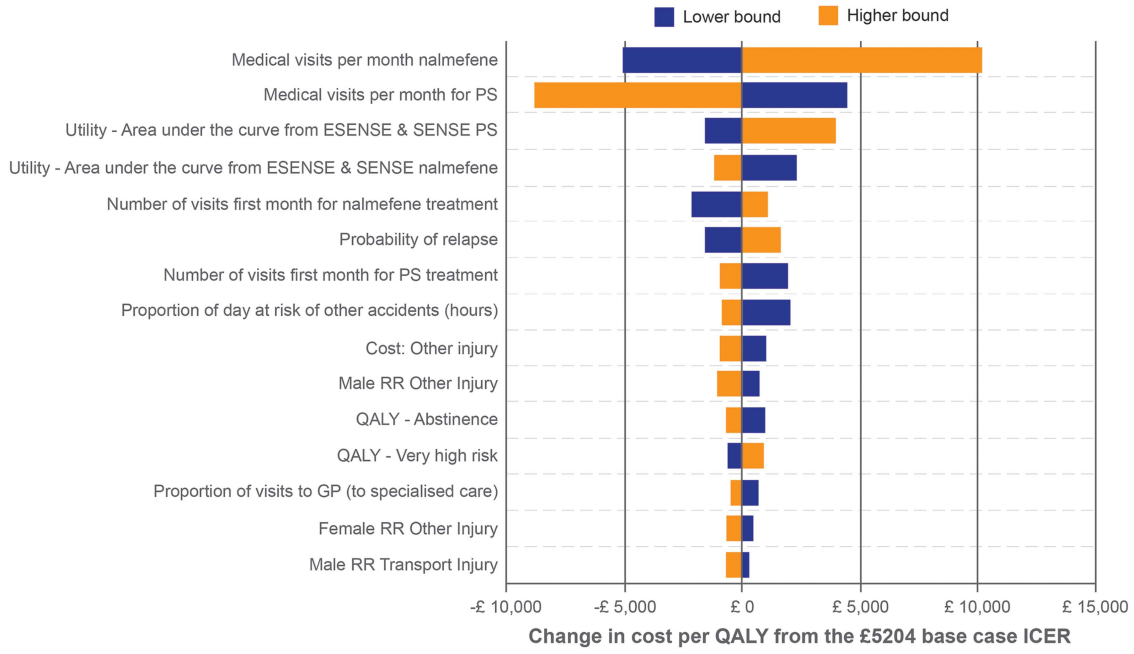

Figure 3 Tornado diagram of the 15 most sensitive parameters in the model (base-case results at 5 years). GP, general practitioner; ICER, incremental cost-effectiveness ratio; PS, psychosocial support; QALY, quality-adjusted life year; RR, relative risk.

Harmful events

A scenario where all harmful events were removed from the model at a 1-year time horizon resulted in a cost per QALY of £29 142 with 24% probability of cost-effectiveness at a £20 000 threshold. This suggests a negligible effect of including these events on the cost-effectiveness results at 1 year. Conversely, excluding these events across a 5-year time horizon caused a more noticeable impact on incremental costs and QALYs compared to the base-case analysis, producing an ICER of £11 530 and 70% probability of cost-effectiveness at a £20 000 threshold.

DISCUSSION

The objective of this economic analysis was to assess the cost-effectiveness of nalmefene plus psychosocial support versus psychosocial support alone for the treatment of nalmefene's licensed population (patients with high/very high DRLs at initial assessment and 2 weeks later). In addition, the analysis aimed to demonstrate the public health benefit of reducing alcohol consumption and the value for the healthcare system of patients entering treatment for alcohol dependence. From the base-case cost-effectiveness assessment, nalmefene had an ICER of £5204 per QALY gained. As the NICE willingness-to-pay threshold is stated to be £20 000–£30 000 per QALY gained, with treatments demonstrating innovation and a high degree of certainty around the ICER being considered at the higher end of this range, nalmefene plus psychosocial support appears to be a cost-effective strategy versus psychosocial support alone.[44] All parameters with statistical uncertainty, including the transition probabilities between drinking levels and dropouts, were varied in the PSA and demonstrated the robustness of the results to this uncertainty. In the OSA, the parameter with the largest impact on cost-effectiveness was increasing the number of medical visits per month in the nalmefene arm from one to two. However, for all analyses the ICER remained below NICE's willingness-to-pay threshold, and nalmefene plus psychosocial support remained a cost-effective strategy.

Nalmefene plus psychosocial support led to the avoidance of 7179 alcohol-attributable diseases or injuries and 309 deaths per 100 000 patients versus psychosocial support alone at 5 years, which represents a considerable benefit. The number of avoided harmful events estimated from this model is likely to be an underestimation of the number of events avoided in real life for several reasons. First, the model used hospital admission data that took into account only the first diagnosis for hospitalisation, while alcohol-dependent patients often have multiple alcohol-attributable conditions diagnosed and managed during the same hospitalisation. It was also assumed that patients can have only one serious event at a time, ignoring the non-negligible possibility of comorbidities. Additionally, when modelling the short-term events it was assumed that patients did not have an additional risk of experiencing these events compared with the general population on days that were not a HDD, suggesting there could be an even larger public health benefit of nalmefene for the treatment of alcohol dependence than that reported in this analysis.

A comparison of the number of alcohol-attributable harmful events avoided with nalmefene plus psychosocial support versus 'no treatment' indicated that there

would be a saving per patient of £193 (95% CI 116 to 304) over 1 year and £845 (95% CI 512 to 1280) over 5 years as a result of these events not occurring (table 10). While nalmefene plus psychosocial support clearly results in a reduction in harmful events compared to no treatment, this was an exploratory analysis to allow a crude estimation of the likely public health benefit of patients being treated for alcohol dependence. As such, the analysis assumed that patients in the 'no treatment' arm remained in a high or very high DRL for the entire time horizon, and did not take into account the possibility that these patients could reduce their level of alcohol consumption without receiving treatment. The number of harmful events occurring with no treatment may therefore have been overestimated. The reduction in number of harmful events with nalmefene plus psychosocial support compared to no treatment appears to be mostly due to the provision of psychosocial support (table 10); however, this observation may be due to overestimation of the number of harmful events occurring with 'no treatment' compared to the other treatment arms. As stated previously, the comparison with a 'no treatment' arm was intended as an exploratory analysis and psychosocial support should be considered a more relevant comparator to nalmefene than 'no treatment', in alignment with current practice in the UK.[8] Finally, even if nalmefene treatment is more costly than psychosocial support alone, we have clearly shown it to be a cost-effective option because of the additional gain in clinical benefit from the drug.

This cost-effectiveness analysis used an innovative approach towards modelling the treatment of alcohol dependence. The model incorporated DRL categories as defined by the WHO and abstinence as main health states, which is a method more sensitive to changes in alcohol consumption than previous models based on the success or failure of treatment. The latter approach was used in developing the NICE clinical guidelines for the treatment of alcohol dependence, whereby NICE explored the relative cost-effectiveness of pharmacological treatments used as first-line treatment for maintaining abstinence in patients with alcohol dependence using two health states related to success and failure.[8] Our approach of using health states for DRLs and abstinence was developed to model the novel use of pharmacological treatment as a first-line option for reducing alcohol consumption in patients with alcohol dependence. This represents a main strength of the present study. A further strength of this analysis was the use of observed patient-level data for modelling multiple health states and, where assumptions were needed, the most conservative option was selected to avoid biasing the model results. Conservative population incidence data and costs were used when modelling alcohol-attributable harmful events, as previously described.

A 5-year time horizon was chosen to evaluate the cost-effectiveness of nalmefene plus psychosocial support versus psychosocial support alone on the basis that this would be sufficient to capture the longer-term consequences of alcohol dependence, while limiting uncertainty from extrapolating data from the current literature. To consider the impact of this decision, a number of scenario analyses were conducted with different time horizons (see online supplementary table J). In the scenario using base-case utilities over a 1-year time horizon, nalmefene plus psychosocial support had a low probability (35%) of being cost-effective compared to psychosocial support alone at a £20 000 per QALY decision threshold (although there was an 89% probability of cost-effectiveness over a 1-year time horizon in a scenario using utilities from the real-world STREAM study). On the other hand, scenarios using a time horizon of 2 years or more had more than 75% probability of being cost-effective at this threshold (see online supplementary table J). This difference was mainly driven by the incremental QALYs accrued after each year in the model (see online supplementary table K). For conservative modelling, the incremental effectiveness between the two treatment arms gained during the first 12 months was retained for the remainder of the model time horizon, represented by the difference at 12 months in the number of patients who had responded to treatment between the compared arms. However, with the exception of the medium DRL health state, no additional differential effect per se between the treatment arms was considered to arise after 12 months. For the medium DRL health state, transition probabilities were extrapolated from the first year of the model and therefore differed between treatment arms (see online supplementary table B). Nevertheless, only a small proportion of patients were in this health state for either treatment arm after the first year, and testing this assumption with an extreme scenario that was unfavourable to nalmefene indicated that the model results were insensitive to this model feature.

For costs, there was a relatively low additional incremental cost from years 2–5, mostly as a result of only 19% of patients returning to treatment each year during this part of the model (from both arms), while the cost of hospitalisation as a result of harmful events remained relatively negligible throughout the model. It is important to note that a 1-year time horizon is not aligned with the NICE reference case regarding the use of an appropriate model time horizon, as alcohol dependence is a chronic disease and 1 year would not be long enough to capture all important differences in costs and outcomes between the interventions being compared.[44] The relevance of considering the long-term consequences of harmful events is further illustrated by the scenario analyses excluding these events (see online supplementary table J); and by the breakdown of cost and QALYs per year per health state categories (see online supplementary table K), where these alcohol-attributable harmful events produced an increasingly more noticeable effect on incremental QALYs and costs from 1 to 5 years.

The nalmefene clinical trials were multinational studies and their use as sources of effectiveness of nalmefene in a UK population may therefore be suboptimal. Nevertheless, the SENSE study included patients from the UK, and these trials are likely to be somewhat generalisable to the UK population given that they captured data on different drinking patterns and cultures across Europe. A comparison of patient baseline characteristics in the nalmefene trials to the UK Alcohol Treatment Trial (UKATT),[45 46] in which almost half of patients opted for alcohol reduction as their treatment approach, suggests that patients were reasonably comparable in terms of age, sex, ethnicity, level of alcohol consumption at study baseline and level of unemployment.

NICE clinical guidelines recommend screening and brief intervention delivered by a non-specialist practitioner as a cost-effective approach for managing hazardous and harmful drinkers.[9] While it could be argued that BRENDA, as used during the nalmefene clinical trials, is not representative of best recommended practice in the UK according to NICE clinical guideline 115 (which recommends cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies as first-line treatment for mild alcohol dependence, aligned with the licensed population for nalmefene),[8 9] BRENDA was deemed by clinical experts to be sufficiently similar to 'extended brief psychosocial intervention', the type of psychosocial intervention used most frequently for patients assessed in standard UK practice, which supports its validity as the main comparator to nalmefene in this model.[32] Furthermore, a reduction in alcohol consumption was observed with the BRENDA plus placebo arm in the nalmefene trials, therefore it does appear to be effective as psychosocial intervention for mild alcohol-dependent harmful drinkers.[14 15]

The quality of life measures used in the nalmefene clinical trials, from which the drinking health state utilities were derived, were EQ-5D data as recommended by NICE for use in cost-effectiveness assessment.[44] However, a systematic review of quality of life instruments in randomised controlled trials for alcohol dependence reported that EQ-5D may not be highly sensitive to outcome changes in alcohol dependence.[47] There could therefore be insufficient correlation between changes in drinking behaviour and alcohol consumption with patient-perceived impact on health status using this measure, which could have led to an underestimation of the QALY gains for nalmefene in this analysis. Utilities from the STREAM study may provide a more realistic QALY assessment than those from the nalmefene clinical trials given that this was a real-world study, whereas the exclusion criteria used in the nalmefene trials could mean that the patients included in these studies were not representative of real life. When considering the scenarios that used utility values from the arguably more realistic STREAM study at 1-year or 5-year time horizons, the incremental QALYs in both cases were higher.

The study was limited by the fact that we considered only direct medical costs of treatment and not the wider impact of alcohol dependence on the population. In addition, we modelled only a limited number of alcohol-attributable harmful events due to limitations in available evidence and the restricted model time horizon. It is likely that further costs to the healthcare system or the patient's quality of life from alcohol-attributable harmful events were not captured by the model. Furthermore, we did not consider ongoing costs beyond the actual acute occurrence of an alcohol-attributable harmful event in the model. For a more comprehensive analysis of the cost-effectiveness of nalmefene, the current model could be extended to include a societal perspective. An extension of the present analysis is currently being conducted with a similar approach to that used in the Sheffield Alcohol Policy Model to estimate the cost of productivity losses to society. This model took into account absence from work and unemployment, as well as the impact of alcohol consumption on the criminal justice system.[19] Finally, while a subpopulation of alcohol-dependent patients from the nalmefene clinical trials with high/very high DRLs was considered in the model, it is often difficult to assess a patient's DRL in clinical practice. In order to optimise the cost-effectiveness of nalmefene plus psychosocial support in clinical practice, appropriate measures to identify patients most suitable for nalmefene (patients with high or very high DRL at initial assessment and 2 weeks later as per nalmefene's indication[11]) are required.

A number of assumptions were made to simplify the model, which could be considered additional limitations. When patients withdrew from or failed treatment, we assumed that they would drink continuously at a high or very high DRL for the remaining model time horizon, instead of providing the opportunity for these patients to enter another treatment option. This assumption is, however, likely to have underestimated the cost-effectiveness of nalmefene, considering the higher proportion of patients who responded to treatment for nalmefene plus psychosocial support compared to the proportion of patients who responded to psychosocial support alone. Using an approach proposed by Barbosa *et al* we also assumed that patients entering the controlled drinking state remained there or relapsed to the high/very high DRLs, without having the possibility of entering the medium DRLs. This was to simplify extrapolation of the within-trial model and was based on data availability. However, as demonstrated in the scenario analyses, the model cost-effectiveness results are driven mainly by the differential effects at year one in the model and refining the long-term phase of the model is not expected to affect the cost-effectiveness conclusions.

NICE recommends that for patients with moderate-to-severe alcohol dependence, treatment should involve medically-assisted alcohol withdrawal followed by psychosocial therapy in combination with

pharmacological treatment to promote maintained abstinence.[8 9] In 2011, NICE published a comparison of two such pharmacotherapies, naltrexone and acamprosate, in terms of relapse rates to heavy drinking after 1 year of treatment in abstinent patients aiming to maintain abstinence.[8] Mean rates of relapse (82.53% for naltrexone; 81.76% for acamprosate) and the uncertainty around the mean rates remained high with treatment. This highlights a potential unmet need in the treatment of alcohol dependence. Nalmefene represents a novel method for treating alcohol dependence by aiming for 'harm reduction' through a reduction in alcohol consumption in non-abstinent patients as opposed to completely abstaining from alcohol. Besides the immediate impact of reducing alcohol consumption, the potential to use nalmefene to prevent patients advancing to more severe alcohol dependence could, in the long-term, lead to a further reduction in alcohol-attributable harmful events and the associated costs. It could also be used to target a previously undertreated population of alcohol-dependent patients by providing an alternative treatment strategy for those who are reluctant to accept abstinence as the treatment goal.

CONCLUSION

In conclusion, results from this cost-effectiveness model comparing nalmefene plus psychosocial support with psychosocial support alone demonstrate nalmefene to be a cost-effective solution for treating alcohol dependence in patients with high/very high DRLs at the £20 000 per QALY gained willingness-to-pay threshold. The results also demonstrate considerable public health benefits of reducing alcohol-attributable harmful events through the use of nalmefene with psychosocial support.

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