The Cost-Effectiveness of the Integration of Nalmefene within the UK Healthcare System Treatment Pathway for Alcohol Dependence

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Abstract

Aims: To assess the cost-effectiveness of integrating nalmefene within the treatment pathway for alcohol dependence recommended by the National Institute for Health and Care Excellence in the UK.

Methods: A Markov model, taking a UK NHS perspective, followed a cohort with alcohol dependence and high/very high drinking risk levels (HVHDRls), who do not require immediate detoxification and who continue at HVHDRls after initial assessment, for 5 years. Costs and quality-adjusted life years (QALYs) from treatment with nalmefene plus psychosocial support versus psychosocial support alone were modelled. The consequent incidence of alcohol-attributable harmful events and disease progression, with the possibility of requiring other options or recurrent treatment, were captured.

Results: Nalmefene plus psychosocial support dominated psychosocial support alone, with lower costs and increased QALYs after 5 years. Savings are driven by the higher response to nalmefene, and the subsequent lower cost accumulation for alternatives.

Conclusions: Nalmefene represents a highly cost-effective treatment option in this population. The analysis shows that integrating nalmefene within the current UK clinical treatment pathway for alcohol dependence could reduce the economic burden on the NHS by limiting harmful events and disease progression.

INTRODUCTION

Alcohol use disorder is characterized by a pattern of compulsive alcohol consumption at a level that interferes with physical, mental and social well-being. Alcohol use disorders have a substantial impact on life expectancy, leading to approximately 2.5 million deaths each year (WHO, 2011b). The health impact and the societal effects of alcohol use disorders place a major economic strain on the individual and society (Rehm et al., 2012).

The risk of developing harms, negative social consequences of alcohol and mortality have all been shown to increase with higher levels of alcohol consumption (Norström, 2002; WHO, 2004; Rehm et al., 2011). In England, the National Institute for Health and Care Excellence (NICE) has published guidelines covering alcohol dependence (NICE, 2010, 2011b). These highlight the importance of early screening and intervention at a mild stage of the disease with brief intervention and psychosocial support to prevent development of more severe disease.

Nalmefene was licensed in 2013 for ‘the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms and who do not require immediate detoxification’ (EMA, 2015). Nalmefene
is to be taken once daily as needed when patients believe they may drink alcohol. Nalmefene was assessed by NICE and found to be cost-effective when added to psychosocial support within its licensed indication (NICE, 2014).

A cost-effectiveness analysis from a UK National Health Service (NHS) perspective has been published finding nalmefene plus psychosocial support to be cost-effective compared to psychosocial support alone with an incremental cost-effectiveness ratio (ICER) of £5204 per quality-adjusted life year (QALY) gained (Laramée et al., 2014). This published model did not, however, consider the full treatment pathway for alcohol dependence recommended by NICE. In particular the published model did not consider the costs and consequences of subsequent treatment and detoxification of patients who fail to respond to treatment with nalmefene plus psychosocial support or psychosocial support only, instead modelling such patients as continuous drinkers for the remainder of the model time horizon.

The population recommended for treatment with nalmefene corresponds to mild alcohol dependent patients defined by NICE (NICE, 2011b, 2014). Such patients failing this first-line treatment option may progress to more severe alcohol dependence, at which point NICE recommends patients receive assisted detoxification and alternative treatment aimed at maintaining abstinence (NICE, 2011b). Given the significant effects of progression to a more severe stage of alcohol dependence in terms of costs and QALYs, an economic model will need to consider effects on subsequent treatment further down the treatment pathway if it is to closely model the effect of adding nalmefene for the treatment of mild alcohol dependence, a perspective not fully captured by the previously published model (Laramée et al., 2014).

The objective of this paper was to build on the previous model by fully integrating nalmefene into the NICE treatment pathway to investigate the costs and benefits of intervention with nalmefene, including delaying or avoiding the development of more severe stages of the disease and the consequent need for further treatments. Additionally, this exercise allows an assessment of how closer modelling of the actual treatment pathway associated with the economic perspective of an analysis may have an important impact on the results and conclusions with respect to cost-effectiveness for healthcare decision makers.

**METHODS**

**Overview**

A Markov model was developed to assess the cost-effectiveness of introducing nalmefene within the treatment pathway for alcohol dependence in England and Wales. The model was created in Microsoft Excel 2010, using a core model structure based on a previously reported Markov approach (Laramée et al., 2014).

In line with the licence for nalmefene and recent NICE recommendation (NICE, 2014; EMA, 2015), the model followed patients with alcohol dependence who continued to have a high or very high drinking risk level (DRL) and no physical withdrawal symptoms following a 2-week assessment period. Patient characteristics were derived from pooled estimates of patients from three Phase III clinical trials of nalmefene: the 6-month ESEN1 study (registered at clinicaltrials.gov as NCT00811720) (Mann et al., 2013; van den Brink et al., 2013), the 6-month ESEN2 study (NCT00812461) (Gual et al., 2012; van den Brink et al., 2013) and the 12-month SENSE study (NCT00811941) (van den Brink et al., 2014), and are the same as those from the previously published model (Laramée et al., 2014).

Two arms were included at the beginning of the model: nalmefene plus psychosocial support and psychosocial support alone. These interventions were modelled using data from the nalmefene plus BRENDA and placebo plus BRENDA arms, respectively, in the clinical trials. BRENDA is a type of psychosocial support developed to promote adherence to treatment and is used to manage chronic behavioural problems in primary and specialist care (Starosta et al., 2006). BRENDA was validated as an appropriate proxy of motivational support and brief intervention in clinical practice, and as a relevant comparator for nalmefene plus psychosocial support by clinical experts as part of the NICE technology appraisal for nalmefene (NICE, 2014).

Whilst the initial nalmefene treatment phase of the model replicates that previously published (Laramée et al., 2014), additional health states and transitions were added to account for patients undergoing assisted detoxification followed byacamprosate or oral naltrexone plus psychological intervention. These features align with guidance from NICE on appropriate treatment of patients who have progressed from mild alcohol dependence to moderate or severe alcohol dependence, for whom a reduction in alcohol consumption is medically unsafe (NICE, 2011b), and with what is envisaged in clinical practice (NICE, 2014). The model consequently evaluated whether adding nalmefene to psychosocial support for alcohol dependence not requiring immediate detoxification influences clinical outcomes such that the economic burden of second-line treatments and alcohol-attributable harmful events over the course of a 5-year time horizon is reduced.

**Model structure**

The 5-year time horizon was modelled as two distinct phases: a 1-year short-term phase followed by a long-term phase lasting 4 years. Within the short-term phase 28-day cycles modelled transitions between five main health states corresponding to abstinence, low, medium, high and very high DRL categories defined by the World Health Organisation (WHO) (Fig. 1) (WHO, 2004). In the long-term phase, the cycle length was extended to 1 year and three main health states were used to represent the level of alcohol consumption. These were ‘controlled drinking’, ‘medium risk drinking’ and ‘high or very high risk drinking’.

In line with the licensed indication for nalmefene (EMA, 2015), patients were initially distributed between the high and very high DRL health states in proportions calculated from pooled nalmefene clinical trial data. Within the first year, at the end of each 28-day cycle, patients transitioned between the five health states at treatment-specific rates informed by the three nalmefene clinical trials. At the start of Year 2, patients in the low DRL or abstinence health states entered the controlled drinking health state, patients in the medium DRL health state entered the medium risk drinking state, and patients in the high or very high DRL health states entered the high or very high risk drinking state. In the controlled drinking health state, patients were assumed to discontinue treatment and remain in this state unless experiencing a relapse in which case they transitioned back into the very high or high risk DRL states in the model’s short-term phase, receiving their originally successful treatment. Patients in the medium risk drinking health state, representing those who partially responded to treatment, continued to receive the same treatment as in the short-term phase of the model. Patients in this health state could transition to either of the other long-term health states at the end of each yearly cycle, on transition probabilities extrapolated from the nalmefene clinical trials (Laramée et al., 2014).

Patients in the high or very high risk drinking state did not respond to treatment and were thus modelled to change to an abstinence-oriented treatment approach in line with NICE guidelines (NICE, 2011b). In the base-case, all of these patients entered a second-line treatment sequence consisting of alcohol withdrawal followed byacamprosate or oral naltrexone plus psychological intervention for
relapse prevention in the form of cognitive behavioural therapies, behaviour therapies, or social network and environment-based therapies delivered at home or in secondary care within an inpatient or outpatient setting (NICE, 2011b) (Fig. 2). Patients successful with second-line treatment moved to an abstinence health state, remaining there unless they experienced a relapse to heavy drinking. Patients who were not successful with this treatment strategy, or who experienced a relapse from the abstinence state, stayed in or entered the high or very high drinking risk state. In the base-case analysis, 50% of these patients remained in the high or very high drinking risk state without receiving further treatment, whereas the other 50% received another round of abstinence treatment. This proportion was varied from 0% to 100% in the one-way sensitivity analysis, as detailed later.

Throughout the model, patients risked dropping out from treatment due to nalmefene-related adverse events or for other reasons such as noncompliance or inefficacy. Patients dropping out due to nalmefene-related adverse events switched to receiving psychosocial support alone (whilst remaining in the nalmefene plus psychosocial support arm). Patients dropping out of either treatment for other reasons entered the high or very high drinking risk state, remaining there until the end of Year 1 when they were provided with the modelled second-line treatment option as those not responding to treatment.

Further health states were defined to reflect the occurrence of alcohol-attributable diseases and injuries known to incur a significant cost to the healthcare system. These events were modelled as tunnel states or permanent post-event states, depending on their pathophysiology of occurrence, using the same methods as in the previously published model (Laramée et al., 2014). The selected events were ischaemic heart disease, ischaemic stroke, haemorrhagic stroke, liver cirrhosis, pancreatitis, lower respiratory tract infections, transport injuries and injuries other than transport. Their predicted alcohol-attributable occurrence was modelled in terms of morbidity (based on hospitalization data) and mortality. Patients were at risk of entering one of these states at the end of each cycle, at health state-dependent rates derived from the published literature (Shield, 2011). Finally, patients could transition to a death state on the occurrence of a fatal alcohol-attributable harmful event or due to all-cause mortality.

**Fig. 1.** Health states and transitions included in the model. *Patients at this stage entered a second-line treatment sequence outlined in Fig. 2. **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 DRL or very high DRL states in the short-term phase of the model), and hence to the original treatment they were successful with.

**Fig. 2.** Second-line treatment sequence to model second-line treatment of patients unresponsive to nalmefene plus psychosocial support or psychosocial support alone.

**Treatment effect**

The model structure was the same for each comparator, with differences in effect being determined by treatment-dependent transition probabilities between the drinking level health states. These differences resulted in treatment-dependent incidences of alcohol-attributable harmful events and determined the proportion of patients responding to treatment or experiencing disease progression and thereby moving to second-line treatment.

Patient-level data from ESENSE1, ESENSE2 and SENSE were pooled to derive the transition probabilities between the drinking level health states and to model treatment discontinuation (Laramée et al., 2014). Further details on the derivation of these transition probabilities are described in Laramée et al. (2014). Relapse from the controlled-drinking state in the long-term phase was estimated to occur at a rate of 19%, using the rationale and source outlined in the previous model (Taylor et al., 1985; Laramée et al., 2014). The same rate was applied for relapse occurring after response to the second-line treatment sequence.
The effect of the second-line treatment options was estimated based on a network meta-analysis conducted by NICE to evaluate the comparative effectiveness of acamprosate or oral naltrexone in conjunction with psychological intervention. The probability of relapsing to heavy drinking at 1 year was calculated as 0.8176 (95% CI 0.3894–0.9996) for acamprosate (NICE, 2011b). Similar effectiveness was demonstrated for oral naltrexone (0.8253 [95% CI 0.4095–0.9997]); it was assumed that the results for acamprosate could be applied for both acamprosate and naltrexine in the model and that this probability would not vary throughout each year.

Risks of experiencing the modelled alcohol-attributable harmful events or death were calculated for each drinking level health state using the same methods as for the previously published model (Laramée et al., 2014). Briefly, data on the level and frequency of alcohol consumption for each drinking level health state were derived from the nalmefene clinical trials and applied to risk equations developed by the Canadian Centre for Addiction and Mental Health (Rehm et al., 2012).

Utilities, costs and resource use
Costs and utility weights were applied to the proportions of patients in each drinking level health state at the end of each cycle. In addition, costs and utility weights or decrements were incurred on the occurrence of alcohol-attributable harmful events.

As in the previous model (Laramée et al., 2014), utility weights for the drinking level health states were derived from EQ-5D scores collected in the ESENSe1, ESENSe2 and SENSE trials. Utilities for alcohol-attributable harmful events were informed by the Sheffield Alcohol Policy Model (Sheffield University, 2009) and Sisk et al. (Sisk et al., 2003), and were applied as a disutility specific to each of the alcohol-attributable harmful events modelled (Laramée et al., 2014) (Supplementary Table S1).

Costs relating to the treatment of alcohol dependence and the management of alcohol-attributable harmful events were considered in the model (Supplementary Table S1). Treatment-related costs included the acquisition price for nalmefene, and the cost of psychosocial support or psychological intervention sessions. Based on clinical opinion, in the base-case analysis 75% of patients were assumed to be treated by general practitioners in primary care, the remainder in specialized care. The cost of psychosocial support provided alone or with nalmefene in primary care was taken as part of a 17.2 minute general practitioner consultation (PSSRU, 2012). When provided in secondary care, the cost was taken as an attendance within specialized drug and alcohol services. These treatment-related costs were estimated from the nalmefene clinical trials and based on current clinical practice in the UK (Gual et al., 2012; PSSRU, 2012; Mann et al., 2013; van den Brink et al., 2013, 2014).

Costs and resource use for the second-line treatment strategy were derived from the NICE CG115 (NICE, 2011a,b). These consisted of the costs for assisted alcohol withdrawal to reach abstinence and pharmacological, medical management and psychological interventions for maintaining abstinence (Table 1).

Costs incurred for managing the alcohol-attributable harmful events were derived from those reported in the Sheffield Alcohol Policy model and the NHS reference cost database (Sheffield University, 2009; NHS, 2012). All costs and outcomes were discounted at a rate of 3.5% per year. Where relevant, costs were inflated to 2012 costs (PSSRU, 2012).

Sensitivity analysis
One-way sensitivity analysis was performed to test the robustness of the model assumptions and uncertainty in all of the individual model parameters apart from transition probabilities between drinking levels and treatment dropouts. This corresponds to 134 parameters. Statistical uncertainty was used to determine the ranges over which parameters were tested, with the standard error used when available (Briggs et al., 2012), or a credible range used otherwise (see Supplementary Table S2 for the list of parameters varied by range of interest). To investigate how the impact of simultaneous uncertainty in the model parameters propagates through to uncertainty in the cost-effectiveness results, probabilistic sensitivity analysis was conducted simultaneously varying all parameters estimated with uncertainty over 5000 iterations. Transition probabilities and utility weights were varied using beta or Dirichlet distributions, relative risks for alcohol-attributable harmful events were varied according to log-normal distributions, and costs were varied using gamma distributions. A list of the parameters varied in the one-way sensitivity analysis and probabilistic sensitivity analysis is presented in the Supplementary material (Supplementary Table S1).

Assuming that all patients who drop out enter the high or very high DRL state is a potentially strong assumption, therefore in order to test the extent to which this assumption affects the model results, a scenario analysis was undertaken. In this scenario, patients dropping out

| Table 1. Unit costs associated with secondary abstinence treatment (NICE, 2011a,b) |
|-----------------------------|-----------------------------|
| Proportion of patients in second-line treatment | Cost |
| Home-based assisted alcohol withdrawal | 43.75%<sup>a</sup> | £595 |
| Secondary care outpatient-assisted alcohol withdrawal | 43.75%<sup>a</sup> | £606 |
| Secondary care inpatient-assisted alcohol withdrawal | 12.5%<sup>a</sup> | £4,145 |
| Weighted average cost of assisted alcohol withdrawal<sup>b</sup> | 100% | £1,044 |
| Pharmacological intervention (acamprosate or oral naltrexone)<sup>b</sup> | 45.5%<sup>d</sup> | £431 |
| Psychological intervention<sup>c</sup> | 45.5%<sup>d</sup> | £741 |
| Total cost of relapse prevention treatment | 45.5% | £1,172 |

<sup>a</sup>Calculated based on NICE CG115 costing report estimates that 14 and 2% of alcohol dependent patients are moderately and severely alcohol dependent, respectively, in England and Wales. It was assumed that moderately alcohol-dependent patients would receive home-based assisted alcohol withdrawal or secondary care outpatient-assisted alcohol withdrawal in equal proportions, and that all severely alcohol-dependent patients would receive assisted alcohol withdrawal in an inpatient setting.

<sup>b</sup>Including the cost of medical monitoring when these interventions are prescribed.

<sup>c</sup>The mean cost of cognitive behavioural therapies, behavioural therapies, and social network and environment-based therapies.

<sup>d</sup>Based on Cochrane reviews, the discontinuation rate from treatment with naltrexone for maintenance of abstinence was 29.1% (877/3011) (Rosner et al., 2010b); and 45.5% (1456/3200) for acamprosate (Rosner et al., 2010a). To reflect discontinuation from these interventions in the model, the higher estimate of 45.5% was applied to the yearly cost of treatment for maintenance of abstinence, being a conservative choice against nalmefene.
for reasons other than nalmefene-related adverse events were assumed to remain in the treatment state which they were in at the time of discontinuation, instead of entering the high or very high DRL as in the base-case.

When adapting the previously published Markov model (Laramée et al., 2014) to reproduce the English treatment pathway, the key change made was to introduce second-line treatment for patients failing psychosocial support with or without nalmefene. A threshold analysis was conducted in which the proportion of patients entering second-line treatment was varied to investigate the influence of this parameter and, in particular, the threshold parameter value at which the model conclusion changed.

RESULTS

Patient evolution through the 5-year time horizon
The proportions of patients across the model health states are presented at each year in Table 2. Lower proportions of patients treated with nalmefene plus psychosocial support compared to psychosocial support alone were in the high or very high DRL states by the end of the first year. Conversely, higher proportions of patients were in the low risk or abstinence health states. Thus the level of alcohol consumption had been reduced in a greater proportion of patients treated with nalmefene plus psychosocial support compared to psychosocial support alone. This effect has a direct impact on the relative proportion of each treatment arm progressing to abstinence-oriented second-line treatment, and this impact was maintained until the end of the model time horizon.

Incidence of alcohol-attributable harmful events
By the end of the 5-year time horizon, 20,474 alcohol-attributable diseases or injuries and 2,502 deaths had occurred in the nalmefene plus psychosocial support arm (n = 100,000), compared to 25,331 diseases or injuries and 2,829 deaths in the psychosocial support alone arm (n = 100,000). A summary of the number of occurrences of each event is presented in the Supplementary material (Supplementary Table S3). Over 5 years, 4,857 diseases or injuries and 327 deaths were therefore avoided by adding nalmefene to the treatment pathway.

Base-case analysis
At the end of 5 years, fewer costs were incurred and more QALYs were gained with nalmefene plus psychosocial support compared to psychosocial support alone (Table 3). Consequently, nalmefene plus psychosocial support dominated psychosocial support alone. The cost savings possible for the NHS from the use of nalmefene within the treatment pathway were driven by lower secondary abstinence treatment costs arising as a result of nalmefene plus psychosocial support preventing progression to more severe levels of alcohol consumption than psychosocial support alone.

Table 3. Incremental costs, life years, QALYs and cost per QALYs for nalmefene plus psychosocial support versus psychosocial support alone, base-case analysis

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<tr>
<th>Year</th>
<th>NMF + PS</th>
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CI, confidence interval; ICER, incremental cost-effectiveness ratio; NMF, Nalmefene; PS, psychosocial support; QALY, quality-adjusted life year.

One-way sensitivity analysis
Of 134 parameters varied in the one-way sensitivity analysis, the 20 parameters that most affected the cost-effectiveness results are presented in the Supplementary material (Supplementary Fig. S1). Overall, the analyses showed that nalmefene remained dominant at the upper and lower bounds of the ICER for 8 of these parameters. The highest ICER for nalmefene plus psychosocial support versus psychosocial support alone from the one-way sensitivity analysis was £11,002/QALY for the upper bound number of medical visits per month for nalmefene.

Probabilistic sensitivity analysis
Results from simultaneously varying the model parameters in the probabilistic sensitivity analysis indicate that uncertainty around the parameters did not alter the conclusion of the base-case analysis that nalmefene is the cost-effective treatment option, with 100% probability that nalmefene plus psychosocial support is a cost-effective alternative to psychosocial support alone at a willingness-to-pay threshold of £20,000/QALY (Supplementary Fig. S2).
Scenario analysis
The results of the scenario analysis conducted to investigate the effect of changing the assumption that patients dropping out would enter the high or very high DRL states are presented in the Supplementary material (Supplementary Table S4). This scenario analysis found nalmefene to be the dominant treatment strategy, as in the base-case results.

Threshold analysis
Nalmefene remained cost-saving when the proportion of patients entering second-line treatment was varied downwards until 91% of patients requiring therapy received it.

DISCUSSION
Integrating nalmefene into the clinical treatment pathway in England
This analysis found that nalmefene plus psychosocial support for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high DRL without physical withdrawal symptoms and who do not require immediate detoxification produced greater QALY gains and lower costs compared to psychosocial support alone. Furthermore, the deterministic and probabilistic sensitivity analyses demonstrate that the results of the present model are robust to uncertainty in the inputs and assumptions, with a probability approaching certainty of the cost-effectiveness of nalmefene plus psychosocial support at the lower NICE threshold of £20,000/QALY for the base-case 5-year time horizon (Supplementary Fig. S2). This result improves on the base-case ICER attained with the earlier model that did not consider the costs of proceeding to second-line therapies after failure to control drinking, demonstrating the impact that considering the treatment pathway specific to the modelled perspective can have (Laramée et al., 2014).

In the UK, only 5.6% of the “in need” alcohol dependent population accesses alcohol treatment each year (Drummond et al., 2005), whilst it is recognized that fewer than 10% of diagnosed alcohol dependent patients in Europe receive treatment (Alonso et al., 2004). Prior to the introduction of nalmefene, the primary treatment goal in the majority of treatment guidelines was abstinence (Mukherjee and Sosa, 2010). For many patients with alcohol dependence, who do not want to stop drinking altogether, abstinence is not an acceptable, or realistic treatment goal (Gastfriend et al., 2007). There is also an unmet medical need for additional treatment options for patients with alcohol dependence who are in an earlier stage of the disease, particularly options that could enhance patient motivation to engage in treatment and obtain better treatment retention resulting in better outcomes. Lack of medication adherence by patients represents an important barrier to effective treatment and may be related to the patients’ disagreement with their disease management and treatment goal (Zwenben et al., 2008). A consequence of poor management, particularly in the earlier stages of alcohol dependence, is that patients might drink more and may therefore be at greater risk of progressing to more severe alcohol dependence, which in turn presents greater risks of harm to the individual and the need for more costly interventions (Norström, 2002; WHO, 2004; Rehm et al., 2011). Nalmefene is well placed to address these unmet needs for those within its licensed indication and this paper has demonstrated that its integration into the clinical care pathway in England and Wales as an option for this subgroup of mild alcohol dependent patients following its recent approval by NICE represents not only an opportunity to improve intervention at earlier stages of the disease but additionally to be cost-saving to the NHS by avoiding progression to more severe stages of the disease and the consequent need for costly second-line treatments.

Model assumptions and limitations
The cost-effectiveness model reported here used a 5-year time horizon, considered sufficiently long to reflect the differences in costs and outcomes between the technologies being compared, without reaching unacceptable uncertainty in terms of patients’ long-term drinking behaviour, treatment needs and future treatment sequence after second-line therapy, and for the development of chronic diseases from long-term alcohol consumption such as cancers. Additionally, this conservatively avoided the assumption that the additional treatment effect observed for nalmefene plus psychosocial support over psychosocial support alone after 12 months (post trials) would remain in the longer term. The probability of relapse was incorporated in the model in a similar manner to a previous model appraising drinking patterns employing transition probabilities derived from a study by Taylor et al. (Taylor et al., 1985; Barbosa et al., 2010). Whilst clinical practice may have changed since the Taylor study was undertaken, the 10-year follow-up of patients in this study and similarity of the patient population to those in the nalmefene clinical trials together with the lack of appropriate studies conducted more recently, make this a reasonable choice. Furthermore, the model results were not sensitive to the relapse probabilities when tested in sensitivity analyses.

The trajectory of patients dropping out from alcohol dependence trials is unknown; therefore it was assumed that patients dropping out of treatment entered the high or very high DRL states. This assumption is strong, but avoided inappropriately assuming an unknown potential maintenance of effect from treatment. Furthermore it was not expected to bias the analysis in favour of nalmefene: pooling the three nalmefene trials, the proportion of patients dropping out for other reasons than adverse events in the nalmefene plus BRENDA arm was 34.6%, while the proportion of all dropouts for the placebo plus BRENDA arm was 36.5% (full analysis set population). Furthermore, the dropout rates observed in higher DRLs were greater for the placebo plus BRENDA arm than for nalmefene plus BRENDA, biasing the analysis against nalmefene. A scenario analysis revealed similar conclusions when patients were modelled to remain in their treatment state at the time of discontinuation.

Relevance and applicability for treatment pathways in other European countries
Both the EU and the WHO have published a series of documents and speeches to highlight the value of reducing harmful alcohol consumption, strongly recommending that national Ministries of Health improve early identification and diagnosis as well as access and delivery of treatment to people suffering from alcohol use disorders (Europa, 2006; WHO, 2010, 2011a, 2012; European Parliament, 2011, 2012). Nevertheless, within the 27 EU countries (plus Norway, Iceland, and Switzerland), 11 have a national treatment guideline for alcohol dependence and 7 have guidelines issued by professional societies, based on which predominant clinical practice can be established (Rehm et al., 2013). Only 2 countries have both national and professional guidelines for the treatment of alcohol dependence (Germany and UK), while 14 countries (including Austria) do not have guidelines published by either of these groups. The lack of optimal treatment guidelines for alcohol dependence in other European countries limits screening, diagnosis and treatment in primary care, and could lead to a lack of motivation to
treat alcohol dependent patients perceived to be difficult and time-consuming by healthcare professionals.

It is recognized that the results and conclusion of this English model cannot simply be generalized to other countries, because of differences in the treatment guidelines and pathways followed in these countries. Nonetheless, the comprehensive clinical pathway provided by NICE, and the subsequent integration of nalmefene into this, provides one of the most comprehensive sets of guidance on the treatment of alcohol dependence in the EU and it may be a worthy model for other countries to review and adapt as appropriate to their national circumstances.

CONCLUSION

Nalmefene plus psychosocial support was dominant versus psychosocial support alone for treating alcohol dependence in those with high/very high DRLs, who do not require immediate detoxification and who continue to have a high/very high DRL after initial assessment. Building upon the previously published assessment (Laramée et al., 2014) to incorporate second-line treatment options as per the NICE clinical pathway reveals the importance of closely modelling the treatment pathway.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Alcohol and Alcoholism online.

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