

Nalmefene (Selincro®) in the management of alcohol dependence

An appraisal report for the Northern (NHS) Treatment Advisory Group

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Summary

- Nalmefene is an oral drug licensed for the reduction of alcohol consumption in adult patients with alcohol dependence and a high level of drinking risk. This represents a novel approach to tackling alcohol dependence in terms of treatment objectives (i.e. reduction vs. abstinence).
- Clinical evidence has demonstrated that significant reductions in total alcohol intake and heavy drinking days were observed in comparisons of nalmefene and placebo, although the effect was inconsistent. The number of monthly heavy drinking days (HDD) was reduced by about 2-3 days with nalmefene compared with placebo. Reduction in daily total alcohol consumption (TAC) was 1.4 units greater with nalmefene compared with placebo in one key study and $\frac{2}{3}$ of a unit in another.
- A more consistent and greater effect associated with nalmefene was identified *post-hoc* in a subgroup defined as those patients who maintained a high drinking risk level for two weeks prior to randomisation. In a pooled analysis of this subgroup the reduction in HDD was around 3 days per month greater with nalmefene compared with placebo and reduction in TAC was nearly 2 units (14 g) per day greater. This is the licensed patient population.
- Although modest the reductions in HDD and TAC were considered clinically relevant by the licensing authority despite divided expert opinions.
- No major safety concerns were identified in the clinical trials although withdrawal rates due to adverse effects were higher with nalmefene than placebo.
- Expected annual treatment costs per patient are broadly in line with other treatments used in the management of alcohol dependence and abuse. Nalmefene is estimated to cost about £400 to £600 per patient per annum although treatment duration may vary.
- Current NICE guidance states that abstinence is the appropriate goal for most people with alcohol dependence. For those with mild dependence without significant comorbidities, and if there is adequate social support, moderate drinking should be considered as a treatment goal. An ultimate goal of abstinence should be encouraged.
- Other licensed medications aim to maintain abstinence rather than reduce consumption.

Introduction

Nalmefene (Selincro®, Lundbeck) is a novel treatment for use in the management of alcohol dependency, available in the UK as a licensed medicine since May 2013. [1] The product license for nalmefene is based on the findings of a *post hoc* subgroup analysis of the published trials [2]. It is licensed 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.

It should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Treatment should be initiated only in patients who continue to have a high drinking risk level two weeks after initial assessment. [1]

A high drinking risk level (DRL) is defined as daily alcohol consumption greater than 60 g for men and 40 g for women. [3] This is equivalent to about 7½ and 5 UK units respectively. [4]

Alcohol use disorders and alcohol dependency

More than 24% of the English population consume alcohol in a way that is potentially or actually harmful to their health or wellbeing. Harmful drinking and alcohol dependence often result in mental and physical health problems as well as wider social problems. The burden on the NHS due to alcohol-related morbidity is substantial. Limiting damage to health from alcohol consumption is a priority for the NHS. [5] A national survey from 2004 found that 4% of people aged between 16 and 64 in England were dependent on alcohol, with a higher prevalence in males than females. The same survey found that rates of alcohol dependence in the North East were among the highest in the country at around 5%. [6]

Alcohol dependence is characterised by craving, tolerance, a preoccupation with alcohol, and continued consumption in spite of harmful consequences. Alcohol dependence is also associated with social issues such as increased criminal activity and domestic violence, and an increased rate of significant mental and physical disorder. [5] Alcohol dependence is classified as mild, moderate or severe depending on a score on the Severity of Alcohol Dependence Questionnaire (SADQ). [7] The SADQ is included in Appendix 1.

NICE guidance states that abstinence is the appropriate goal for most people with alcohol dependence. For those with mild dependence without significant comorbidities, and if there is adequate social support, moderate drinking should be considered as a treatment goal. Harm reduction should also be considered a treatment goal for those with more severe alcohol dependence who refuse to consider abstinence, though an ultimate goal of abstinence should still be encouraged. [5]

A combination of pharmacological and psychological interventions aiming to promote abstinence and prevent relapse is recommended for people with moderate or severe alcohol dependence. Patients with mild dependence do not usually require pharmacological intervention and first line management should be with psychological intervention. NICE guidance states that pharmacological intervention may be required for those with mild

dependence who do not respond to psychological intervention alone, or who specifically request pharmaceutical intervention. [5]

Nalmefene

Nalmefene is an opioid receptor modulator with antagonistic activity at two specific receptor subtypes, and partial agonist activity with a different receptor subtype. Nalmefene is believed to reduce alcohol consumption by down-regulating the reinforcing effects of alcohol through modulation of dopamine dependent reflexes. [1,8,9]

Nalmefene should only be prescribed following an initial visit at which the patient's clinical status, alcohol dependence, and level of self-reported alcohol consumption should be evaluated. Patients should then record their alcohol consumption for approximately two weeks. [1]

At a subsequent visit nalmefene may be initiated in patients with high DRL as observed over this two-week period. Nalmefene must be used in conjunction with psychosocial intervention focused on treatment adherence and reducing alcohol consumption. [1]

A patient's response to treatment and the need for continued pharmacotherapy should be evaluated on a regular basis, for example a monthly interval. [1]

Dosage

Nalmefene is to be taken as-needed. Patients are required to perceive their risk of drinking alcohol each day. If they consider themselves at risk of alcohol consumption on that day they should take one 18 mg tablet, preferably 1 to 2 hours prior to the anticipated time of drinking. If the patient has commenced alcohol consumption without taking nalmefene on that day then they should take one tablet as soon as possible. The maximum dose is one tablet per day. [1]

Clinical evidence

The efficacy and safety of nalmefene in alcohol dependence has been evaluated in two similar six-month randomised controlled trials known as ESENSE1 and ESENSE2. A further 1 year randomised controlled trial known as SENSE was also conducted. All three studies were double-blind, parallel-group and placebo-controlled in design. The two ESENSE studies have been published in peer reviewed journals. [8,10] The SENSE study has not been published to date although data has been made available in via an abstract and poster. [2,11]

Inclusion criteria for the ESENSE studies were: age \geq 18 years, diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition text revision and blood alcohol level $<$ 0.02% at screening. Exclusion criteria were extensive and included: $<$ 6 heavy drinking days per month (HDD), less than medium DRL, $>$ 14 consecutive abstinent days in the month prior to screening, a need for immediate detoxification, severely abnormal liver enzymes, psychiatric disorders and a range of concomitant medications. [8,10] A large number of patients reduced their levels of alcohol intake to below the eligibility criteria prior to randomisation.

In both ESENSE studies both treatment groups received a psychosocial intervention (BRENDA) during the 1st, 2nd, and 4th weeks and monthly thereafter. This focused on treatment adherence and reduction of alcohol consumption. See appendix 2. [12]

Both studies also utilised the same predefined co-primary outcome measures which were the change from baseline in HDD and total daily alcohol consumption (TAC) in grams at month six. Daily alcohol intake was assessed through self-reporting.

ESENSE 1 [8]

770 individuals were screened and 604 were randomised to receive 24 weeks of nalmefene 18 mg (n = 306) or placebo (n = 298) when required.

Statistically significant differences in HDD and TAC was observed consistently from month one onwards. Mean HDD decreased from 19 to 8 days in the nalmefene group and from 20 to 11 days with placebo at month six (between group difference in favour of nalmefene: -2.3 days [95% confidence interval: -3.8 to -0.8]; p = 0.002)

Mean TAC at month six was reduced from 84 to 33 grams in the nalmefene group and from 85 to 45 grams in the placebo group (between group difference of 11.0 g in favour of nalmefene [95%CI: -16.8 to -5.1]; p = 0.003). One UK unit of alcohol is equivalent to about 8 g therefore this represents a reduction of about 1.4 units per day, or nearly 10 units per week.

A substantial proportion of study participants (54% of nalmefene and 32% of placebo recipients) withdrew from the study. In the active treatment group this was predominantly due to adverse effects.

ESENSE 2 [10]

941 individuals were screened and 718 were randomised to receive 24 weeks of nalmefene 18 mg (n = 358) or placebo (n = 360) when required.

A statistically significant difference in HDD was observed from month one onwards. A statistically significant difference in TAC was observed only at months 1, 2, 3 and 5.

At month six, mean HDD decreased from 20 to 7 days in the nalmefene group and from 18 to 8 days in the placebo group at month 6 (between group difference in favour of nalmefene of -1.7 days [95%CI: -3.1 to -0.4]; p = 0.012).

At month six, mean TAC reduced from 93 to 30 grams in the nalmefene group and from 89 to 33 grams in the placebo group (between group difference in favour of nalmefene of -5.0 grams [95%CI: -10.6 to 0.7]; p = 0.088).

A large number of withdrawals and a large number of patients who reduced their levels of alcohol intake to below the eligibility criteria prior to randomisation may limit the validity of these results and the integrity of the randomisation.

The primary outcomes of the ESENSE studies are summarised in table 1. Note that this is a different patient population to that for which nalmefene is licensed.

Although a significant effect with respect to TAC was not identified in the primary analysis a *post hoc* analysis conducted in a subgroup of patients who maintained high risk drinking between screening and randomisation (n = 214) did detect a significant benefit associated with nalmefene. *Post-hoc* analyses from both studies are described in table 2.

Post hoc pooled subgroup analysis [2]

In both ESENSE studies there were marked reductions in drinking risk level between screening and randomisation in about half of all study participants despite the absence of any pharmacological or psychological intervention during this period. At the point of randomisation there will have been reduced potential for further reductions in alcohol intake in these patients. This is known as the 'floor effect'. Consequently a target population was defined *post hoc* to be those who had continued to have high or very high drinking risk level at both screening and randomisation (n = 667).

The consistently high drinking risk subgroup of 667 participants included 335 randomised to receive nalmefene and 332 to placebo. Results are summarised in table 2. Note that these analyses relate specifically to the licensed patient population.

Table 1. Primary outcome measures for all patients from the ESENSE studies [8,10]

	ESENSE1		ESENSE2	
	Nalmefene	Placebo	Nalmefene	Placebo
Baseline HDD	19 days	20 days	20 days	18 days
6 month HDD	8 days	11 days	7 days	8 days
HDD change (nalmefene vs. placebo)	-2.3 days [95%CI: -3.8 to -0.8]; p = 0.002		-1.7 days [95%CI: -3.1 to -0.4]; p = 0.012	
Baseline TAC	84 g	85 g	93 g	89 g
6 month TAC	33 g	45 g	30 g	33 g
TAC change (nalmefene vs. placebo)	-11.0 g/day [95%CI: -16.8 to -5.1]; p =0.0003		-5.0 g/day[95%CI: -10.6 to 0.7]; p =0.088	

Table 2. Post hoc subgroup analysis of primary outcome measures for the licensed population from the ESENSE studies [12]

	ESENSE1		ESENSE2		Pooled analysis	
	Nalmefene n = 85	Placebo n = 114	Nalmefene n = 103	Placebo n = 111	Nalmefene n = 188	Placebo n = 225
Baseline HDD	23 days	23 days	23 days	22 days		
6 month HDD	9 days	14 days	10 days	12 days	-12.6 days	-9.4 days
HDD change (nalmefene vs. placebo)					-3.2 days [95%CI: -4.8 to -1.6]; p < 0.001	
Baseline TAC	102 g	99 g	114 g	108 g		
6 month TAC	40 g	57 g	44 g	52 g	-65.7 g	-51.4 g
TAC change (nalmefene vs. placebo)					-14.3 g/day [95% CI: -20.8 to -7.8], p < 0.001	
Study treatment consumption					58%	72%

n = number of patients in each group who contributed values at month 6. All study non-completers have been assumed to be non-responders.

One year study (SENSE) [11]

The SENSE study has not yet been fully published in peer reviewed literature and caution should therefore be expressed in drawing any conclusions from the study data.

Primary outcome objectives were defined as safety and tolerability over twelve months, and efficacy over six months of nalmefene 18 mg per when required, compared with placebo. The study comprised 675 participants, randomised to receive nalmefene (n = 509) or placebo (n = 166). As with the ESENSE studies [8,10] efficacy was assessed through self-reported HDD and TAC. The study did not identify a statistically significant effect for nalmefene compared with placebo in reducing HDD ($p = 0.160$) or TAC ($p < 0.232$) at six months.

HDD and TAC were both reduced at one year compared with baseline in both groups, with the reduction significantly greater with nalmefene compared with placebo. However efficacy at 12 months was not a primary outcome measure and the available abstract does not indicate the number of patients remaining in the study at 12 months or the basis of the efficacy population.

A subsequent poster presented a *post hoc* analysis of data from the SENSE trial including only those patients with high DRL at both screening and randomisation. This cohort comprised 187 participants (n = 145 with nalmefene, and n = 42 with placebo). [13] A substantial proportion of these participants (33% placebo and 47% nalmefene) withdrew from the study at some point. Efficacy analyses were based on those who were treated and had a valid post-baseline assessment (n = 141 and n = 42 at baseline, and n = 78 and n = 29 at month 13, respectively). There was no statistically significant reduction in HDD measured at month six although a statistically significant difference was present from months 7 to 13. At month 13, HDD reduction was 3.6 days greater with nalmefene than with placebo (95%CI: -6.5 to -0.7 days, $p = 0.016$). The difference in TAC reduction was statistically significantly greater with nalmefene than with placebo at all time-points from two to 13 months. At 13 months TAC reduction was 17.3 g (~2 units) greater with nalmefene than with placebo (95%CI: -30.9 to -3.8 days, $p < 0.013$). [13]

Safety

In ESENSE1, [8] adverse events (mostly mild or moderate) and dropouts due to adverse events were more common with nalmefene than placebo. During the main treatment period, 198 patients in the placebo group (67%) and 246 patients in the nalmefene group (81%) had treatment-emergent adverse events. The dropout rate was significantly different between groups ($p < 0.0001$); the most frequent primary reason was withdrawal of consent in the placebo group and adverse events in the nalmefene group. The number of patients with serious adverse events was similar in both treatment groups. [8]

Similar safety outcomes were reported in ESENSE2. [10] Most adverse effects were mild or moderate and were more common with nalmefene than placebo. During the main treatment period 199 placebo patients (59%) and 232 nalmefene patients (68%) had treatment-emergent adverse events. The most common treatment-emergent adverse events (nausea, dizziness, and insomnia) had an incidence two times greater with nalmefene than with placebo. The dropout rate due to treatment emergent adverse events was similar in both

treatment groups. Serious adverse events were reported in 17 placebo patients and eight nalmefene patients. [10]

In the pooled analysis of the ESENSE studies [2] in the high risk population about 77% of nalmefene patients had one or more adverse events. The most commonly reported adverse events associated with nalmefene were dizziness, nausea and insomnia. The corresponding result with placebo was about 67%. 17.5% of nalmefene patients dropped out due to adverse events compared with 8% of placebo patients. Serious adverse events were reported in 12 patients in the placebo group and 15 patients in the nalmefene group. [2]

Summary of clinical evidence

The clinical significance of the apparent treatment effect of nalmefene on the reported outcome measures is unclear. The difference in effect sizes between the total population and licensed population was about one heavy drinking day per month and less than one unit difference in daily total alcohol consumption.

The Committee for Medicinal Products for Human Use (CHMP) considered the observed treatment effects in the ESENSE studies (Table 1) to be small, inconsistent and of uncertain clinical relevance. [9] Nalmefene did not receive a licence based on the whole randomised study population, instead the license is based on the findings of a *post hoc* subgroup analysis in the high risk drinking level sub-group. The conclusion was that 'however modest, the effect size of nalmefene was clinically meaningful'. [9]

It is interesting to note that the CHMP report is accompanied by a divergent position statement in which six signatories stated '*There is no direct evidence of harm reduction*' and '*The majority of participants continued to have significant levels of HDD and daily levels of consumption of alcohol. The clinical significance of this modest reduction in alcohol consumption has not been demonstrated in these studies*'. [9]

The results from all nalmefene studies in alcohol dependence demonstrate a high treatment effect in both treatment groups suggesting that psychosocial support alone may be an effective treatment. The reduction from baseline in the placebo group is considerably greater than the incremental reduction associated with nalmefene. The incremental benefit from nalmefene is small albeit in a notoriously hard-to-reach and highly morbid patient group.

Although statistical significance was demonstrated, confidence intervals are relatively wide and at the lower end would be of questionable clinical relevance. The large number of patient withdrawals and large number of patients who reduced their levels of alcohol intake to below the eligibility criteria prior to randomisation may limit the validity of the results and the integrity of randomisation.

The subgroup was not defined due to withdrawal rates but due to a significant and presumably unexpected participant behaviour change between screening and randomisation.

Pharmacoeconomic analysis

Prices do not include VAT unless otherwise indicated

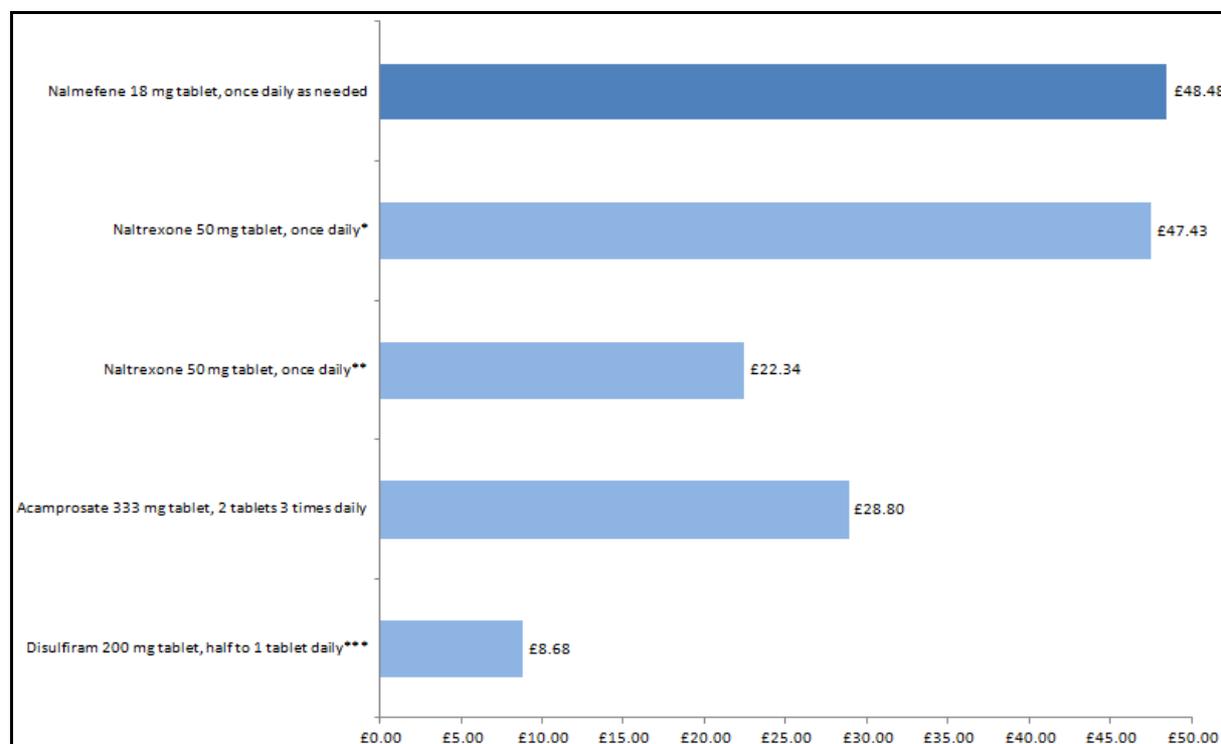
The cost of nalmefene is £42.42 per 14 tablets. [14] Based on a usage rate of 60% as observed in the pooled analyses the cost of 28 day's treatment is about £49. [15]

Other licensed medications for use in alcohol dependence include acamprosate, naltrexone and disulfiram. These pharmacological interventions are recommended by NICE to support abstinence from alcohol. [5]

Figure 1 demonstrates the comparative cost for 28 day's treatment at recommended doses for each of the therapies and nalmefene. [15] Therapeutic equivalence has not been robustly tested and is not implied.

A recent NICE Evidence Summary stated that the manufacturer of nalmefene estimated the number of people treated with nalmefene in England & Wales to be 5,779 in year 1 rising to 65,778 in year 5, based on unrestricted prescribing access. The manufacturer estimated the cost per person for 1 year of treatment to be £385 based on 1 tablet every 2 to 3 days. The corresponding total costs for England & Wales are £2,223,817 for year 1 and £25,312,032 in year 5. [15] The frequency of nalmefene usage in clinical trials was around 60% of days; higher than the rate used for this estimate.

Figure 1. Cost of 28 days of treatment of alcohol dependence [15]



* Most expensive brand. ** Cheapest brand & drug tariff price.

*** Initial dose is 1 tablet daily for 5 days

Points to consider

The clinical evidence for nalmefene in alcohol dependence demonstrated high levels of efficacy in both active and placebo treatment groups, suggesting that the concomitant psychosocial intervention was itself highly effective. The incremental benefit of nalmefene in the licensed population was modest being of the order of about 1 or 2 fewer units of alcohol consumed per day, and three fewer heavy drinking days per month. Benefits may accumulate.

The clinical studies were confounded by high drop-out rates and significant participant behavioural change between screening and randomisation. A post-hoc analysis identified a cohort of persistent high drinking risk level patients for whom nalmefene was considered to be clinically effective.

Nalmefene is specifically licenced for use only in patients with a high DRL. A high or very high DRL is representative of mild to moderate alcohol dependence. [9]

Clinical data for the use of nalmefene under randomised controlled conditions are available for a period of 6 to 12 months. Caution is therefore advised if prescribed for more than 1 year.

NICE recommends that the ultimate goal for alcohol dependency should be abstinence. NICE is expected to issue technology appraisal guidance concerning nalmefene in November 2014.

There is a lack of evidence to indicate whether nalmefene-mediated reductions in HDD or TAC will enable the target patient group with alcohol dependence to ultimately achieve a goal of abstinence.

Nalmefene should be prescribed as part of a wider programme which must include psychosocial interventions targeted at alcohol dependence (see appendix 2). Use of nalmefene in the absence of such is unlikely to be effective and would be outside of the product license.

In common with other medications licensed for use in alcohol dependence, nalmefene should only be used in combination with psychosocial support. The form of psychosocial support provided in the clinical trials was the BRENDA intervention, which focused on treatment adherence and reduction of alcohol consumption. [12] It was provided at 0, 1 and 2 weeks, then monthly and was itself associated with a substantial decrease in HDD and TAC, compared with baseline. The scale of reduction from baseline with placebo was a greater than the additional benefit associated with the addition of nalmefene. Given the scale of effect attributed to the psychosocial intervention used in the clinical trials, clarification is needed to determine whether this can be replicated locally in order to support a complete package of care.

Although a relatively high rate of adverse effects was reported in both the active and placebo treatment arms, causality has not been established. Alcohol dependent patients may experience effects from reduced alcohol consumption in the absence of nalmefene or any other pharmacological intervention. Some specific effects did appear to be more common with nalmefene than with placebo, such as nausea, dizziness and insomnia, although the majority were mild or moderate in severity.

Exclusion criteria for the clinical trials comprised mental health disorders and therefore evidence is lacking on the safety and efficacy of nalmefene in this group of patients. Mental health disorders are common comorbid conditions in those with alcohol use disorders and caution must therefore be exercised if nalmefene is used in such patients.

Lundbeck is supporting a number of initiatives to develop relevant services in primary care settings. These include supporting healthcare professionals training in assessment and psychosocial support as well as developing an online psychosocial support tool which will be free of charge to patients. [15]

Nalmefene has expected annual treatment costs of about £400 to £600 per patient per annum based on usage rates observed in clinical studies. Patients may not require treatment for as long as one year. Real usage rates may vary from those observed in clinical studies. Nalmefene is priced at a similar level to other pharmacological treatments used in the management of alcohol dependency and abuse.

Nalmefene has been recommended by the Scottish Medicines Consortium and the All Wales Medicines Strategy Group (preliminary recommendation). [16, 17]

Author's declaration

The author has no relevant interests or potential conflicts to declare. The report editor has participated in advisory boards and similar, and other non-promotional events, directly and indirectly on behalf of pharmaceutical companies which may have included Lundbeck or competitor companies.

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Appendix 1. Severity of alcohol dependence questionnaire (SADQ)

The SADQ questions cover the following aspects of dependency syndrome: [7]

- Physical withdrawal symptoms
- Affective withdrawal symptoms
- Relief drinking
- Frequency of alcohol consumption
- Speed of onset of withdrawal symptoms.

Respondents answer 'almost never', 'sometimes', 'often' or 'nearly always' to each of the following questions. Questions 17 & 18 are slight variations, with responses of 'not at all', 'slightly', 'moderately' and 'quite a lot'.

Responses attract a score in the following manner.

- Almost never / not at all: 0
- Sometimes / slightly: 1
- Often / moderately: 2
- Nearly always / quite a lot: 3

A total score is produced and is interpreted in the following manner.

- 31 or higher indicates "severe alcohol dependence"
- 16-30 indicates "moderate dependence"
- 16 or less usually indicates only a mild physical dependency

During [a defined] period of heavy drinking

1. The day after drinking alcohol, I woke up feeling sweaty.
2. The day after drinking alcohol, my hands shook first thing in the morning.
3. The day after drinking alcohol, my whole body shook violently first thing in the morning if I didn't have a drink.
4. The day after drinking alcohol, I woke up absolutely drenched in sweat.
5. The day after drinking alcohol, I dread waking up in the morning.
6. The day after drinking alcohol, I was frightened of meeting people first thing in the morning.
7. The day after drinking alcohol, I felt at the edge of despair when I awoke.
8. The day after drinking alcohol, I felt very frightened when I awoke.
9. The day after drinking alcohol, I liked to have an alcoholic drink in the morning.
10. The day after drinking alcohol, I always gulped my first few alcoholic drinks down as quickly as possible.
11. The day after drinking alcohol, I drank more alcohol to get rid of the shakes.
12. The day after drinking alcohol, I had a very strong craving for a drink when I awoke.
13. I drank more than a quarter of a bottle of spirits in a day (OR 1 bottle of wine OR 7 beers).
14. I drank more than half a bottle of spirits per day (OR 2 bottles of wine OR 15 beers).
15. I drank more than one bottle of spirits per day (OR 4 bottles of wine OR 30 beers).
16. I drank more than two bottles of spirits per day (OR 8 bottles of wine OR 60 beers)

Imagine the following situation

You have been completely off drink for a few weeks. You then drink very heavily for two days. How would you feel the morning after those two days of drinking?

17. I would start to sweat.
18. My hands would shake.
19. My body would shake.
20. I would be craving for a drink.

Appendix 2. BRENDA

BRENDA therapy consists of six components: [12]

- **Biopsychosocial evaluation**
- **Report to the patient on assessment**
- **Empathic understanding of the patient's situation**
- **Needs collaboratively identified by the patient and treatment provider**
- **Direct advice to the patient on how to meet those needs**
- **Assess reaction of the patient to advice and adjust as necessary for best care**

The first two components, evaluation and report, constitute what is typically recognised as a 'brief intervention'. The BRENDA structure requires for further understanding and discussion with the patient with a view to developing a plan. The precise details of the BRENDA therapy employed within the nalmefene studies has not been ascertained for this report.