Single Technology Appraisal (STA)

Nalmefene for the reduction of alcohol consumption in people with alcohol dependence [ID660]

MANUFACTURER'S RESPONSE TO CLARIFICATION LETTER DATED 21ST MARCH 2014

Literature searching

- **Please provide justification (including limitations) for restricting the literature searches to English language studies only.**

In our manufacturer's submission (MS) we have undertaken three literature reviews and below we discuss each in turn. Wherever possible, our approach was informed by literature reviews undertaken for the purposes of developing previous NICE guidelines, specifically CG115 and CG100.

In CG 100 the NICE guideline development process excluded all non-English references:

> "Systematic literature searches were undertaken to identify evidence within published literature in order to answer the clinical questions. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters. Non-English language studies were not reviewed and were therefore excluded from searches." (Ref: NICE CG 100. Alcohol-use disorders: diagnosis and clinical management of alcohol-related physical complications. 2010. Page 8).

Nalmefene literature review

In terms of the studies assessing nalmefene, we are fully confident that we have included and language has not filtered out any references. We have complemented the review of the published literature and have provided in the MS the list of all unpublished evidence available and its relative impact on the MS decision problem (please refer to Figure B1 of the MS on page 65 titled "Flow diagram of identification process for systematic review of nalmefene studies").

Psychosocial interventions review

When we scoped out this review we identified the potential to return a large number of hits. So we decided a pragmatic approach would be to update the existing systematic review from NICE CG115. Using the same approach as for CG100 noted above, non-English language publications were excluded. The approach taken in CG115 was also used to inform our search strategy for the psychosocial interventions literature review.

In addition, we believe that the specific cultural context for trials assessing such interventions may be an important consideration for the applicability of the outcomes to the English and Welsh context.

For this reason, we consider that limiting this review to English-language studies would have a negligible impact on an appropriate assessment of the STA decision problem. We have, however, been back to the review process and identified that only one non-English

article was excluded at level 1 screening (Ekinci A, Ekinci O, Turkcarpar H, Ozbay H. Emotional schemas and their relationship with clinical characteristics in patients with alcohol dependence. Noropsikiyatri Arsivi 2012;49(4):286-93). No non-English articles were excluded at screening level 2. Upon rescreening, this article was excluded as being a non-randomised study (only randomised studies were included at screening level 2).

Naltrexone

We recognise that reviewing naltrexone studies published in languages other than English could benefit the STA decision problem. We have thus revisited this review to identify the non-English studies captured by our search. During the level 1 screening process, 35 non-English studies were captured and can be excluded based on their titles and abstract for the reasons detailed in Appendix 1. At level 2 screening, a total of 18 non-English articles were excluded. Upon rescreening, all these studies were excluded for the reasons detailed in Appendix 2. We therefore conclude with confidence that our review of naltrexone has captured all the relevant evidence available and is appropriate to the STA decision problem.

Section A: Clarification on the treatment pathway

A1. Priority Question: Please clarify why the economic model does not take into account the recommendations in NICE clinical guideline 115 (see points a-c below). Please provide an indicative incremental cost-effectiveness ratio where nalmefene is used only in those patients who did not respond to psychological interventions as recommended in the NICE clinical guideline.

a. The 'general principles for all interventions' section of the NICE clinical guideline 115 states that 'all interventions for people who misuse alcohol should be delivered by appropriately trained and competent staff.'

The economic model does take into account the principle that all interventions for people who misuse alcohol should be delivered by appropriately trained and competent staff, for following reasons:

Lundbeck's survey of primary care (tier 2) and specialist services (tier 3) confirmed that primary care practices routinely manage patients with mild alcohol dependence and other alcohol disorders at the less severe end of the spectrum. Generally speaking, these patients were not considered in need of referral to the local Community Alcohol Team or in need of detoxification. NICE public health guidance already recommends that health and social care professionals providing care for people at risk of hazardous and harmful drinking in NHS-commissioned services should receive training in providing alcohol screening and structured brief advice and if there is local demand, should also be trained to deliver extended brief interventions (NICE. Alcohol-use disorders: preventing harmful drinking (PH 24) 2010). Furthermore, the NICE Quality Standard 11 recommends that healthcare professionals ensure they opportunistically carry out screening and brief interventions for hazardous and harmful drinking as an integral part of practice and on a routine basis (NICE Quality Standard 11. Alcohol Dependence and harmful alcohol use. August 2011).

Nalmefene does not require specialist initiation. It can be both initiated and used in primary care and community settings without any requirement for additional testing beyond what is usually performed for patients diagnosed with alcohol dependence. The

Scientific Advisory Group consulted by the European Medicines Agency also endorsed the prescribing of nalmefene by general practitioners (GPs). This allows patients with mild dependence to access treatment in a setting appropriate to their needs and circumstances, as proposed by the NICE Commissioning Guidance (NICE. Services for the identification and treatment of hazardous drinking, harmful drinking and alcohol dependence in children, young people and adults. Commissioning guide. 2011). Furthermore, nalmefene can be delivered by any suitably qualified and trained healthcare professional within their usual clinical practice, irrespective of care setting. Thus, this would include healthcare professionals working in specialist, secondary care, primary care and community-based settings, all of whom may be competent to prescribe nalmefene.

The nalmefene Summary of Product Characteristics (SmPC) requirement for continuous psychosocial support should be considered part of a standard clinical interaction and not a significant change from what would be delivered in common practice (Volpicelli et al., 2001; Johnson et al., 2003; Pettinati et al., 2004; Pettinati et al., 2005; Starosta et al., 2006). Continuous psychosocial support is a simple intervention and is very similar to what is commonly used in routine clinical practice for the management of other long-term or chronic conditions, such as diabetes, where the patient's involvement in decisions about his or her own management and care is important. In these circumstances, healthcare providers address a wide variety of behavioural problems in their patients and routinely manage chronic diseases with a combination of clinical advice and support (that is, feedback together with expressing caring, encouraging progress, providing a positive reinforcement attitude, and educating the patient on the disease) and medication management.

The components of continuous psychosocial support required by the nalmefene SmPC can therefore be delivered by primary care practitioners with appropriate knowledge in the treatment of alcohol dependence during a routine consultation, with support from local community-based non-statutory alcohol services (Rome, 2014a). English expert clinical opinion has confirmed this view. Specialist alcohol services would also have the appropriate knowledge to provide these components of psychosocial support as recommended in the Quality Standard Statement 4 "People accessing specialist alcohol services receive assessments and interventions delivered by appropriately trained and competent specialist staff".

The cost-effectiveness analysis included cost interventions by healthcare providers using usual NHS reference costs as described in the Manufacturer's Submission (MS). No cost has been considered for healthcare providers training for delivering alcohol misuse interventions. We believe that one may consider that this cost relates to a future step for the implementation of optimal NHS intervention and outside the remit of the cost-effectiveness assessment. Furthermore, we believe that this cost, because it would need to be applied to both compared treatment cohorts, would not affect the conclusion of the base case cost-effectiveness results. Additionally, we consider that the implementation of training costs would be minimal when broken down at individual patient level with respect to a cost-effectiveness evaluation. This has been informed by the cost-effectiveness analysis presented in the NICE CG 100 (Alcohol-use disorders: diagnosis and clinical management of alcohol-related physical complications) assessing dosing regimens for acute alcohol withdrawal interventions (page 223, Appendix 3). In this analysis, the cost of implementing the alcohol misuse-related intervention of 'symptom-triggered regimen' was considered. The implementation included the cost of training healthcare providers who will manage patients, and the supervision cost post-training for doing so. This cost has been demonstrated to be negligible when calculated at a patient level: cost of training per healthcare provider per

patient = £0.14; supervision cost post-training per healthcare provider per patient = £0.11.

b. In section 1.3.3 of the NICE clinical guideline 115 it is stated that acamprosate or naltrexone can be prescribed for those that have not responded to a psychological intervention alone, or those that have specifically requested a pharmacological intervention.

The recommendation made in section 1.3.3 of NICE Clinical Guideline (CG) 115 for people with mild alcohol dependence was for a use of naltrexone and acamprosate that was unlicensed and based on limited evidence.

NICE CG 115 (full version) states: "Due to limited literature in this [harmful & mild dependent] population, a meta-analysis of RCTs could not be conducted. […] The Guideline Development Group (GDG) considered that given the limited evidence to support the use of naltrexone to reduce drinking in non-dependence or mild dependence that it should only be used where psychological interventions alone have not been effective. It should be prescribed in conjunction with a psychological intervention. Although no direct evidence was identified for acamprosate, the GDG considered the equivalence of acamprosate and naltrexone in *moderate and severe* dependence and decided that it was reasonable to extrapolate from this data and also recommend acamprosate for use in this group."

The guideline recommendation for the unlicensed use of naltrexone and acamprosate in mild dependence was therefore based on limited evidence. The recommendation was also made before nalmefene was available to be considered as a suitable evidence-based, licensed pharmacological option for patients with mild dependence. In this context it is worth noting the General Medical Council (GMC) direction to use a licensed medicine whenever possible (http://www.gmc-uk.org/guidance/ethical_guidance/14327.asp).

The decision problem for this STA relates to the indicated use of nalmefene in the reduction of alcohol consumption in patients with alcohol dependence. Neither acamprosate nor naltrexone is licensed for the goal of reduction of alcohol consumption. Acamprosate is not included in the scope for this appraisal for the reason noted in the Block Scoping Report for Batch 31 (nalmefene); the marketing authorisation for acamprosate states "treatment should only be initiated after weaning therapy, once the patient is abstinent from alcohol". The Report also states "It was agreed that the comparators in the scope should be amended to include naltrexone in combination with psychological support for certain people who have mild alcohol dependence as well as psychological support alone." Clinical expert feedback suggests naltrexone and acamprosate are not established standard of care treatment for newly-diagnosed patients with mild alcohol dependence. Furthermore naltrexone, if used in mild dependence at all, would be used to reduce cravings in order to reduce the risk of relapse from abstinence, and not for the reduction of alcohol consumption without previously achieved abstinence, which is a very different treatment goal. Even when naltrexone is prescribed for patients with mild alcohol dependence, it is done so in mild dependent patients who have previously failed detoxification and who need support to help them maintain an abstinent state. To be prescribed nalmefene, a patient must be actively drinking.

In the cost-effectiveness analysis, naltrexone and acamprosate are offered to patients failing their first line treatment: that is, psychosocial intervention alone, or nalmefene + psychosocial intervention. This later comparison is the heart of the decision problem of

the STA with regard to the available data for nalmefene for its use as first-line treatment (post brief intervention) with psychosocial intervention in the assessed population of patients, as opposed to the non-availability of data for acamprosate and naltrexone. The second-line treatment option proposed with naltrexone or acamprosate in the cost-effectiveness analysis includes an alcohol withdrawal intervention. This gives consideration to the likelihood of the evolution of patients' disease severity during the process of the failed first-line intervention. This takes into account the evidence available for naltrexone and acamprosate in the context described in the CG 115. Nevertheless, removing this alcohol withdrawal intervention cost would not affect the overall conclusion of the analysis. Further details of this explanation are given in our response to priority question A2.

c. **Section 1.3.3 of the NICE clinical guideline 115 also relates to delivering psychological interventions. This states that therapies should usually consist of one 60-minute session per week for 12 weeks.**

Lundbeck's survey of primary care (tier 2) and specialist services (tier 3), conducted specifically to support the evidence base for this STA, showed that only 20-30% of patients with mild alcohol dependence were offered therapies at a level of intensity consisting of one 60-minute session per week for 12 weeks. The vast majority of mild dependent patients (80-100%) were routinely offered 'Brief Intervention' and/or "Extended Brief Intervention', irrespective of treatment setting.

A 'Brief Intervention' is the mainstay of treatment in primary care. In most of the geographical areas covered by the survey, this 'Brief Intervention' consists of brief advice, given by the GP or practice nurse, to cut down or abstain from drinking. In some areas, but not all, the Brief Intervention is supplemented by a variety of low-intensity offerings, including psychosocial support of an unspecified nature, group therapy, a physical health check with or without blood tests and/or vitamin supplementation. The clinical experts we consulted confirmed that the survey findings were in accordance with their understanding of clinical practice in England for managing people with mild alcohol dependence.

Extended brief interventions would be appropriate level of psychological interventions for treating mild dependence in a generalist tier 2 setting (Raistrick 2006, P85 CG115 full).

The type of psychosocial support required when prescribing nalmefene for patients with mild dependence is continuous psychosocial support focused on treatment adherence and reducing alcohol consumption (Nalmefene SmPC, 2013). The components of continuous psychosocial support can be delivered by primary care practitioners with appropriate knowledge in the treatment of alcohol dependence during a routine consultation, with support from local community-based non-statutory alcohol services (Rome, 2014a). Continuous psychosocial support is a simple intervention and is very similar to what is commonly used in routine clinical practice for the management of long-term or chronic conditions. In these circumstances, healthcare providers address a wide variety of behavioural problems in their patients and routinely manage chronic diseases with a combination of clinical advice (that is, feedback together with expressing caring, encouraging progress, providing a positive reinforcement attitude, and educating the patient on the disease) and medication management. Thus, the psychosocial support recommended with the use of nalmefene in the SmPC can be delivered during a usual medical consultation in primary care/tier 2 and/or in tier 3 services.

In the cost-effectiveness model, we have conducted a scenario analysis which compares nalmefene + psychosocial intervention versus psychosocial intervention consisting of one 60-minute session per week for 12 weeks.

For the nalmefene arm, we kept the same management pattern of the base case analysis for the psychosocial intervention provided with nalmefene. This highlights that treatment with nalmefene not only gives the option of adding a pharmacological treatment as first-line treatment (post brief intervention) to psychosocial intervention, but also gives the option of a lower-threshold psychosocial intervention - with motivational support that can be given at primary and secondary care levels as part of a usual medical consultation.

For the treatment cohort with psychosocial intervention consisting of one 60-minute session per week for 12 weeks, we have implemented the patient management element in the following way, informed by the economic analysis undertaken for CG115:

- It was assumed that each patient would receive 12 60-minute sessions delivered by a practice nurse. This was costed as £91 per hour of client contact (PSSRU 2012). This was applied during the first 12 weeks of the model in considering patient drop-outs equal to that observed during the nalmefene clinical trials.

- It was assumed that patients would all require one initial 30-minute outpatient consultation with a consultant psychiatrist prior to starting treatment. This was costed as £202 (£605/3) (PSSRU 2012).

This scenario analysis resulted in nalmefene + psychosocial intervention still dominating psychosocial intervention alone, leading to even more savings (see scenario 1 of Table 1 below).

We tested a second scenario where psychosocial intervention alone was costed as described above (scenario 1 in Table 1 below), but now assuming that 100% of patients treated with nalmefene + psychosocial intervention are treated by a specialist. This does not change the conclusion of the base case that nalmefene + psychosocial intervention dominates (see scenario 2 of Table 1 below).

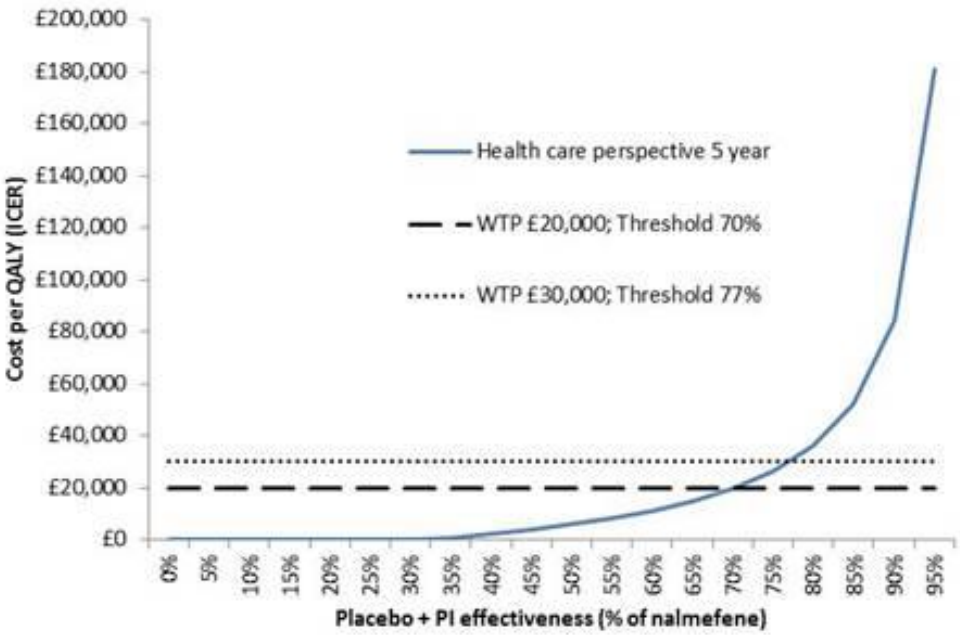
Table 1

Scenario	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
	NMF + PI	PI alone	NMF + PI	PI alone			
Base case	£4,445	£4,842	3.624	3.553	-£397	0.071	Nalmefene dominates
SCENARIO 1	£4,445	£5,933	3.624	3.553	-£1,488	0.071	Nalmefene dominates
SCENARIO 2	£4,874	£5,933	3.624	3.553	-£1,059	0.071	Nalmefene dominates

In terms of providing an indicative ICER when nalmefene is used only in those patients who did not respond to psychological intervention, the clinical data available on nalmefene allows the precise estimation of the cost-effectiveness of the use of nalmefene as first line treatment in addition to psychosocial intervention, compared to psychosocial intervention alone. There are no data available allowing a precise assessment of nalmefene as a second line treatment for patients failing psychosocial intervention.

However, as investigated in Scenario 7 of the MS (section 7.7.10 of the MS), the cost-effectiveness of nalmefene + psychosocial intervention was robust to a substantial increase of effect of psychosocial intervention alone (decrease of relative effect between cohorts). As shown in Figure 1 below, the treatment effect of psychosocial intervention would need to have an increased treatment effect of 70% to 77% (for a willingness-to-pay threshold of £20,000 and £30,000) for nalmefene + psychosocial intervention not to be cost-effective compared to psychosocial intervention alone. Thus, there would need to be a significant decrease in relative effect between nalmefene + psychosocial intervention and psychosocial intervention alone, beyond 70% to 77%, for the implementation of nalmefene + psychosocial intervention not to be cost effective compared to psychological intervention, as second line treatment for patients failing psychosocial intervention. We do not believe this is probable.

Figure 1



A2. Priority Question: Please clarify whether the clinicians whose advice was used to assume 12 months of <u>psychosocial</u> intervention or psychosocial intervention + nalmefene before considering naltrexone were based in England. The ERG's clinical advisers indicate that people would not be allowed to remain in the very high or high drinking risks for this length of period before naltrexone was used. They suggest 3 months is more likely. Please clarify the likely impact of this assumption on the cost-effectiveness ratio.

Lundbeck sought specific advice in relation to this NICE STA submission from clinical experts practising in and/or based in the NHS in England. The treatment sequence (p46 of the MS) on which the economic model is based shows that mild dependent patients who remain at high or very high Drinking Risk Level (DRL) in the first year, but who need assisted withdrawal/detoxification, would be referred for withdrawal assessment and follow the treatment pathway on the right-hand side of the diagram for detoxification and relapse prevention treatment supported with acamprosate or naltrexone in conjunction with psychological interventions. In this scenario, we do not disagree with the expert advisers to NICE that patients with a high DRL could be treated with naltrexone after a

period of three months, *if* they had withdrawal symptoms. However, this is not the nalmefene population.

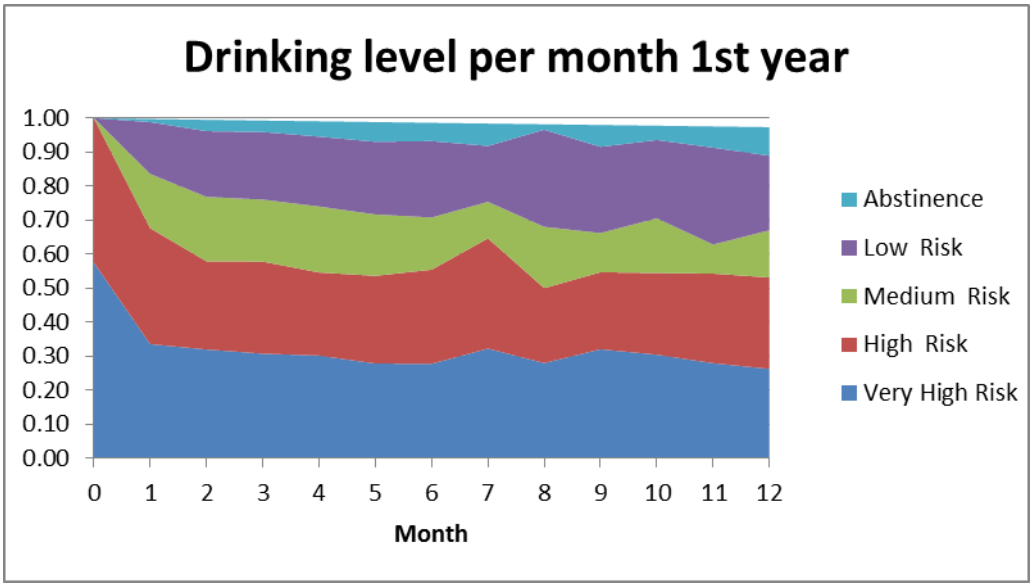
For mild dependent patients who remain at high or very high DRL but who do *not* require assisted withdrawal/detoxification in the first year, the clinical experts' advice to Lundbeck was that these patients would be treated further with psychological intervention or with psychological intervention + nalmefene, in preference to psychological intervention + unlicensed naltrexone. Furthermore, the need to undertake a 'naloxone challenge test' and for ongoing liver function testing when prescribing naltrexone use was given as a further reason why its use is unlikely in a primary care/tier 2 setting. Clinical experts in Wales also supported this view, when advising the All Wales Medicines Strategy Group on the use of nalmefene. As stated in the MS and above, primary care/tier 2 is the most appropriate setting for treating patients with mild dependence who do not require detoxification given their clinical and other needs (NICE Commissioning Guidance, 2011).

The base case cost-effectiveness results, which consider a second-line treatment option with naltrexone/ acamprosate for patients having failed initial treatment with nalmefene + psychosocial support or psychosocial support alone (patients drinking at high/ very high level at 1 year), shows nalmefene + psychosocial support dominating psychosocial support alone (incremental QALY=0.071, incremental cost=−£397) (MS page 239). When removing the option of the second-line treatment and assuming that patients drinking at high/ very high level at 1 year continue to drink at that level up to 5 years; this results in an ICER of £5,090 per QALY gained (incremental QALY=0.086, incremental cost=£438) (MS page 243).

The base-case analysis concluded that nalmefene + psychosocial support is cost-saving compared with psychosocial support alone. This can be explained by the higher proportion of responders at 1 year for the nalmefene arm, and thus fewer patients going onto a costly second line treatment applied the same way for compared treatment cohorts.

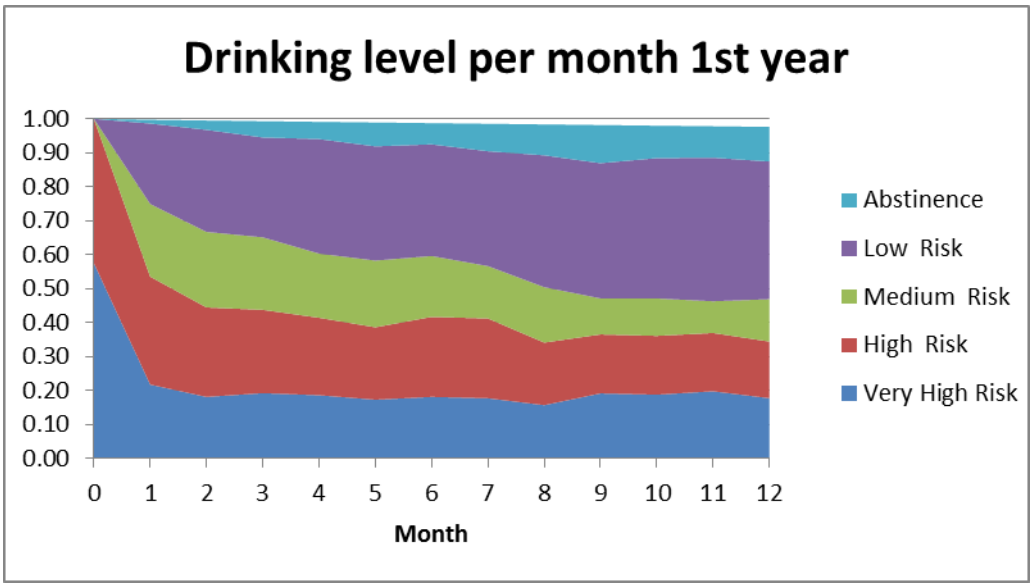
If we assume in the model that treatment failure with nalmefene + psychosocial support or psychosocial support alone is defined by patients remaining at high/very high DRL for a period of 3 months before naltrexone/acamprosate is considered, this incurs earlier and additional costs over the 5 year time horizon of the model, a time horizon which encounters for multiple courses of treatment for some patients. Comparing the treatment cohorts, the incremental is to favour nalmefene with regard to the different monthly proportions for compared arms of patients drinking at high/ very high DRL over the first year of the model, as shown during the nalmefene clinical trials (Figure 2 and Figure 3). The result of this assumption is therefore to favour nalmefene + psychosocial support even more, compared to psychosocial support alone.

Figure 2. Proportion of patients, per WHO DRL, for PI, year 1 of the model (Figure B25 of the MS, page 232)



DRL = drinking risk level; WHO = World Health Organization.

Figure 3. Proportion of Patients, per WHO DRL, for nalmefene + PI, year 1 of the model (Figure B26 of the MS, page 233)



DRL = drinking risk level; WHO = World Health Organization.

A3. Priority Question: The ERG's clinical advisers also indicate that maintaining patients on nalmefene beyond 12 months may be unlikely in those reduced to moderate risk levels. Additionally the Summary of Product Characteristics also states that '*Caution is advised if Selincro is prescribed for more than 1 year'.* Please clarify the implication of altering this assumption on the incremental cost-effectiveness ratio.

To investigate the assumption of all patients being in the medium drinking health state after 1 year of treatment continuing with nalmefene, three scenario analyses have been performed. In these analyses, the following alternative assumptions of treatment pathways have been investigated:

Scenario 1: Patients in the medium drinking health state are assumed to not have responded to treatment and relapse back to high/ very high DRL and thus change treatment strategy to an abstinence-orientated approach (second-line treatment option).

Scenario 2: Patients in the medium drinking health state are assumed to have responded to treatment and are modelled in line with other patients having responded to treatment in the controlled-drinking health state.

Scenario 3: An extreme scenario against nalmefene where patients in the medium drinking health state in the nalmefene + psychosocial intervention arm are modelled to have not responded (as scenario 1) and patients in the psychosocial intervention alone arm are modelled to have responded (as scenario 2).

All three scenarios showed that the cost-effectiveness conclusion is not sensitive to varying this model feature. Table 2 below details the results for the three tested scenarios. For scenario 3, extreme scenario against nalmefene, the ICER is still well below the £20,000 threshold.

Table 2. Scenario investigating varying the assumption of all patients being in the medium drinking health state after 1 year of treatment continuing with nalmefene

Scenario	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
	NMF + PI	PI alone	NMF + PI	PI alone			
Base case	£4,445	£4,842	3.624	3.553	-£397	0.071	Nalmefene dominates
Scenario 1	£4,803	£5,240	3.608	3.538	-£437	0.070	Nalmefene dominates
Scenario 2	£4,218	£4,559	3.638	3.570	-£341	0.068	Nalmefene dominates
Scenario 3	£4,803	£4,559	3.609	3.570	£244	0.039	£6,280

The clinical experts advising Lundbeck indicated that the decision to maintain patients on nalmefene beyond 12 months would be based on clinical judgement based on each patient's situation.

A4. Please provide details on potential complications of individuals taking nalmefene with other opiates. For example, the use of over the counter medicines such as cough medicine that contain codeine, or the use of opiates in the event of an accident.

The Selincro (nalmefene) SmPC includes in Section 4.3 Contraindications: patients taking opioid analgesics and patients for whom recent use of opioids is suspected. The use of nalmefene with opiates is therefore contraindicated in these circumstances.

Nalmefene's pharmacodynamic profile as an opioid system modulator, with antagonistic activity at the mu and delta receptors and partial agonist activity at the kappa receptor, means that when it is taken concomitantly with opioid agonists such as certain cough and cold preparations and antidiarrhoeal medicinal products containing codeine, the patient may not benefit from the use of the opioid agonist.

The same rationale applies to the use of nalmefene with both weak and strong opioid analgesics. Consequently, the SmPC states (Section 4.4 Special warnings and precautions for use) that the product should be temporarily discontinued for one week prior to the anticipated use of opioids, for example, if opioid analgesics might be used during elective surgery.

If opioid analgesics are required to be administered to a patient currently receiving nalmefene in an emergency situation, the amount of opioid required to obtain the desired effect may be greater than usual. Consequently, the risk of opioid-related side effects, including respiratory depression, may be increased and the patient should be closely monitored for the emergence of any adverse reactions in these circumstances. The nalmefene SmPC states that if opioids are required in an emergency, the dose must always be titrated individually and if unusually high doses are required, close observation is necessary.

Furthermore the nalmefene SmPC advises prescribers to advise patients that it is important to inform their healthcare professional of their last intake of nalmefene if opioid use becomes necessary.

Section B: Clarification on the effectiveness data

B1. Please clarify if study selection, data extraction and quality assesment were undertaken independently by a minimum of two reviewers for each of the three systematic reviews (pharmacological interventions, psychosocial interventions and cost-effectiveness). If not, please explain why.

We can confirm that study selection (level 1 and level 2 screening) was performed independently by two researchers. All disagreements between the researchers were resolved by consensus, with input from a third experienced senior researcher if necessary.

Data extraction and quality assessments were performed by one researcher and reviewed by a second researcher. This was undertaken for all three of the systematic literature reviews.

B2. Please provide a detailed breakdown of all excluded full text studies (that is, full reason for exclusion and reference) for the systematic reviews of nalmefene and naltrexone.

Appendix 3 presents a detailed breakdown of all full-text articles excluded from the systematic reviews of nalmefene and naltrexone. All foreign-language (non-English) articles were rescreened and excluded for reasons other than language (see Table 1 and Table 2 above).

B3. Please provide further details (for example, number of patients with alcohol dependency, length of abstinence prior to randomisation, efficacy [baseline, final, difference and safety results], if relevant) on the following nalmefene studies in the European Public Assessment Report by each treatment arm which were excluded from the submission to NICE: CPH-101-801 (Karhuvaara et al), CPH-101-701 (unpublished) and CPH-101-299 (Anton et al., 2004). In addition, the Karhuvaara et

al. study included a a large group of heavy drinkers (93%) that met the criteria for alcohol dependence. Please clarify why evidence from this (or other similar) studies would not be useful given the majority of alcohol dependent people

As described on page 29 of the MS, five studies in alcohol-use disorders were conducted previously by Biotie Therapies Corporation, and that as part of a development programme for nalmefene, these studies suggested that nalmefene could be effective in reducing alcohol consumption and provided the rationale for the further development of the nalmefene 18 mg dose (EMA, 2012). Of important note, these studies were considered by the EMA during the regulatory process only to support nalmefene development to its current indication, *as the design and context of these studies were not aligned with the licensed indication for nalmefene* (EMA, 2012).

As shown in page 64-65 of the MS, all five Biotie-sponsored studies (2 published and 3 unpublished) were excluded from the review at the level 2 screen, the main reasons for exclusion were study population, use of nalmefene outside its indication, and study design. We would like to emphasise that even if the Karhuvaara et al. study included a large group of heavy drinkers (93%) that met the criteria for alcohol dependence, the specificity of the nalmefene target population being focused on patients “who continue to have a high DRL 2 weeks after initial assessment”, represents an important patient characteristic leading the beneficial effect of nalmefene, and that this was not assessed as such by Karhuvaara et al. Thus this is limiting the value of Karhuvaara et al. results for the decision problem (this in addition to the other study characteristics limiting its applicability to the decision problem in England as shown in Table 3 below: flexible dosing for nalmefene; study conducted in Finland only). On the other hand, the Karhuvaara et al. study is positive in demonstrating the efficacy of nalmefene. Nevertheless, we strongly believe that the listed limitations for the use of the Karhuvaara et al. study for the decision problem makes this study inappropriate to be included in the cost-effectiveness modelling; if so being to lead to unforeseen uncertainty that would limit the robustness of the cost-effectiveness analysis.

For giving more information as requested on the Biotie studies, please see below Table 3: Table 10-1 of the MS (page 277-278, Appendix 2), to which we have added a further column with the requested information.

Table 3. Biotie-sponsored studies evaluating nalmefene in alcohol-use disorders (Table 10-1 page 277-278 of the MS, Appendix 2).

Trial and publication	Intervention, comparator, population, study design, and primary efficacy outcome measures	Relevant to the scope of the submission?	Requested additional information
CPH-101-0801 (Karhuvaara et al., 2007)	• Nalmefene flexible doses of 10 mg, 20 mg, or 40 mg as-needed (n = 242) • Placebo + biopsychosocial assessment feedback and advice (n = 161) • Patients drinking heavily who had difficulties in controlling drinking • Randomised, double-blind, parallel-group, placebo-controlled, 28 weeks (+24 weeks run-out), multicentric, single-country (Finland) • Monthly number of HDDs	No. Population not limited to alcohol-dependent patients; flexible dosing for nalmefene; study design limited the generalisation of the results (single-country).	[redacted]

Trial and publication	Intervention, comparator, population, study design, and primary efficacy outcome measures	Relevant to the scope of the submission?	Requested additional information
CPH-101-0701 (unpublished)	• Nalmefene flexible doses of 10 mg, 20 mg, or 40 mg as-needed (n = 84) • Placebo + biopsychosocial assessment feedback and advice (n = 82) • Patients who had a desire to reduce and gain better control of alcohol consumption; had difficulties in controlling drinking plus a family history of alcohol problems • Randomised, double-blind, parallel-group, placebo-controlled, 28 weeks, multicentric, single-country (UK) • Monthly number of HDDs	No. Population not limited to alcohol-dependent patients; flexible dosing for nalmefene; 75% of premature discontinuation for nalmefene group and 66% for placebo group (median time, 40 days for nalmefene and 61 days for placebo). This and the low number of patients randomised limited the validity of the study outcomes; study design limited the generalisation of the results (single-country).	[redacted] [redacted] [redacted] [redacted]

Trial and publication	Intervention, comparator, population, study design, and primary efficacy outcome measures	Relevant to the scope of the submission?	Requested additional information
CPH-101-0299 (Anton et al., 2004)	• Nalmefene fixed doses (5 mg/day, 20 mg/day, or 40 mg/day) for 12 weeks followed by as-needed dosing in a 40-week extension (n = 202) • Placebo + manual-guided MET (n = 68) • Patients with alcohol dependence diagnosed according to DSM-IV and abstinent prior to treatment initiation • Randomised, double-blind, parallel-group, placebo-controlled, 12 weeks + 40-week extension period, multicentric, single-country (US) • Monthly number of HDDs	No. Patients required to be abstinent prior to treatment initiation; nalmefene daily dosing for the first 12 weeks.	[redacted]

Trial and publication	Intervention, comparator, population, study design, and primary efficacy outcome measures	Relevant to the scope of the submission?	Requested additional information
CPH-101-0399 (unpublished)	• Nalmefene 10 mg or 40 mg daily dosing (n = 100) • Placebo (n = 50) • Patients who had difficulties in controlling drinking • Randomised, double-blind, parallel-group, placebo-controlled, 16 weeks, multicentric, single-country (Finland) • Monthly number of HDDs	No. Population not limited to alcohol-dependent patients; nalmefene daily dosing; the use of unapproved doses.	[redacted]
CPH-101-0400 (unpublished)	• Nalmefene flexible doses of 10 mg, 20 mg, or 40 mg as-needed (n = 60) • No placebo arm • Patients who had difficulties in controlling drinking • Open-label, uncontrolled study, 52 weeks, multicentric, single-country (Finland) • Monthly number of HDDs	No. Population not limited to alcohol-dependent patients; flexible nalmefene dosing; open-label study design.	[redacted]

Trial and publication	Intervention, comparator, population, study design, and primary efficacy outcome measures	Relevant to the scope of the submission?	Requested additional information
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HDD = heavy drinking day; MET = motivational enhancement therapy; UK = United Kingdom; US = United States.			

B4. Please provide the evidence source for the following statement in Table B8 (page 78; final column): 'the TFLB method…has been widely used in clinical studies and has been shown to give reliable retrospective self-reports of drinking in outpatients'.

Please find below five references relevant to this topic:

Babor TF, Steinber K, Anton R et al. Talk is cheap: Measuring drinking outcomes in clinical trials. J Stud Alcohol 2000 Jan;61(1):55-63

Maisto SA, Sobell MB, Mitch Cooper A and Sobell LC. Test-Retest reliability of retrospective self-reports in three populations of alcohol abusers. J Behav Assessment 1979; 1(4):315-26

Maisto SA, Conigliaro JC, Gordon AJ, McGinnis KA, Justice AC. An experimental study of the agreement of self-administration and telephone administration of the Timeline Followback interview. J Stud Alcohol Drugs 2008 May;69(3):468-71

Sobell LC, Sobell MB. Alcohol timeline followback (TLFB). In: Rush AJ, First MB, Blacker D, editors. Handbook of psychiatric measures. Arlington, VA: American Psychiatric Publishing Inc.; 2008

European Medicines Agency. Guideline on the development of medicinal products. 2010

B5. Please provide the reasons for withdrawal for patients that were randomised but not treated in ESENSE1 (Figure B4; page 88), ESENSE2 (Figure B5; page 89) and SENSE trials (Figure B6; page 90).

Two patients were randomised but not treated in ESENSE 1; for the nalmefene patient the primary reason for withdrawal was to 'non-compliance' while for the placebo patient the primary reason for withdrawal was 'lost to follow'.

Seven patients were randomised but not treated in ESENSE 2; 3 nalmefene patients (one patient actually completed the 24 weeks treatment period) and 4 placebo patients. The primary reason for withdrawal for the 2 nalmefene patients were 'withdrawal of consent' and 'other, specified as *the patient said he could not continue the study due to personal problems (family)*' while for the placebo patients the primary reason for withdrawal was 'withdrawal of consent' (2 patients), 'lost to follow' and 'other, specified as *patient has been confirmed to be alive, but did not return to the site to complete the study'*.

One nalmefene patient was randomised but not treated in SENSE, the primary reason for withdrawal was 'other, specified as *primary finding of hepatitis C infection*'.

B6. Please provide tabulated outcome data for all outcomes (including sample size) for each treatment arm of the ESENSE1, ESENSE2 and SENSE trials as baseline (±SD), final (±SD), mean difference from placebo, 95% confidence intervals and p values for continuous outcomes or by event rates, odds ratios, 95% confidence intervals and p values for binary data.

Tabulated outcomes data are presented in Appendix 4. Please note that, for continuous outcomes, we have presented "Change from Baseline (SE)" instead of "Value at final (SD)" as the study endpoints were pre-specified as "Change from Baseline".

B7. Please clarify why a meta-analysis of the safety and efficacy evidence using individual patient level data or aggregate data for all outcomes of interest was not undertaken. A pooled analysis primarily focuses on treatment groups rather than on studies and this approach does not consider the validity of the comparisons; thus it is subject to confusion bias (also known as Simpson's paradox).

[redacted]

Table 3: Pooled analysis using patient level data adjusted on country. Changes from Baseline to Month 6 in HDDs (days/month) (FAS) – Patients with a High or Very High DRL at Baseline and Randomisation

HDDs (days/month)	**Change from baseline to Month 6**		**Difference to NMF-PBO**		
Study					
Treatment Group	**N**	**Mean ± SE**	**Mean ± SE**	**95% CI**	**p-value**
ESENSE 1, ESENSE 2, SENSE					
PBO	[redacted]	[redacted]			
NMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Pooled analysis using patient level data adjusted on country. Changes from Baseline to Month 6 in TAC (g/day) (FAS) – Patients with a High or Very High DRL at Baseline and Randomisation

TAC (g/day)	Change from baseline to Month 6		Difference to NMF-PBO		
Study					
Treatment Group	**N**	**Mean ± SE**	**Mean ± SE**	**95% CI**	**p-value**
ESENSE 1, ESENSE 2, SENSE					
PBO	[redacted]	[redacted]			
NMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B8. The baseline characteristics of people within ESENSE1 and ESENSE2 differed (Table 10-8; page 287), as did the effect size of nalmefene. Please clarify whether any analysis was undertaken to determine if any of the characteristics were treatment effect modifiers.

The populations in ESENSE 1 and ESENSE 2 were very similar, with only minor differences in the demographic characteristics despite the fact that the studies were conducted in different regions of Europe. The patients in ESENSE 1 were slightly older than those in ESENSE 2 (52 *versus* 45 years) and the ratio of men to women was 2:1 in ESENSE 1 and nearly 3:1 in ESENSE 2. Comparison of results in subpopulations (include gender and age) was performed in the total population based on the pooled data for ESENSE 1 and ESENSE 2; these analyses demonstrated robustness and internal consistency of the data. No treatment effect modifiers were identified other than WHO DRL.

B9. Please clarify whether any factors were considered as random in the mixed model repeated measures analysis and what interaction terms were investigated.

The primary analysis for the co-primary efficacy variables was a mixed model repeated measures (MMRM) analysis using all available data measured over each month during the treatment period. The MMRM analysis provides an unbiased estimate of the treatment effect under the assumption that missing data are missing at random.

The MMRM model used observed cases (OC) and included the baseline value as a covariate and site (grouped sites), sex, time in months (Months 1 to 6), and treatment as fixed effects. The baseline value-by-time interaction and treatment-by-time interaction were also included in the model; an unstructured covariance matrix was used.

B10. Please clarify why the pooled effects analysis did not consider weighting for within and between study variability.

The pooled effect analysis was done on patient level data and therefore the within-study variability can be considered as adequately handled.

Since the studies were conducted in mutually exclusive list of countries for the different nalmefene clinical trials, a country adjustment was deemed more accurate than an adjustment on study because of being more reliable to handle the between-study variability.

B11. Please clarify the specific assumptions that are being made when evaluating the different methods of imputation of missing data. Please explain why the mixed model results are assumed to be valid when they are said to be based on "patients adhering to treatment" (page140).

The mixed model repeated measures (MMRM) analysis uses all available data measured over each month during the treatment period and provides an unbiased estimate of the treatment effect under the assumption that missing data are missing at random (MAR). Published data support the validity and robustness of the MMRM analysis regarding protection against type I error and against bias, also in situations with a non-negligible proportion of missing data. Using extensive simulations, it has been demonstrated that the type I error is only affected to a limited extent and that the bias is small under the assumption that a third of the missing data are missing-not-at-random, even when there is a severe imbalance between the treatment groups in the proportion of withdrawals (reference to Siddiqui O, Hung HMJ, O'Neill R. MMRM vs LOCF: A comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat 2009; 19: 227-246). To clarify, the MAR assumption implies that the behaviour of the post dropout observations can be predicted from the observed variables; thus the model does not assume that *"patients adhere to treatment"*.

There is no single solution for how to handle missing data; therefore, several sensitivity analyses were performed. These were: analyses of covariance (ANCOVAs) using observed cases (OC), the last observation carried forward (LOCF), the baseline observation carried forward (BOCF) and placebo mean imputation (PMI). The OC, LOCF and BOCF analyses approaches are standard and often used to address missing data. The PMI approach imputed the reduction at Month 1 in the placebo group to all timepoints with missing data; the reduction at Month 1 was chosen because all patients in the FAS contributed to the Month 1 estimation. This approach may be considered very conservative and unlikely to be biased in favour of nalmefene, as it did not take into account the continued reduction in alcohol consumption after Month 1 in the placebo group. The multiple imputation (MI) approach assumes that patients who withdraw differ from those who complete the study and that imputed outcomes (conditional on the past) are the same as those in the placebo group (with the same past). The MI approach minimises the difference between the treatment groups and possibly yielding a deflated estimate of the treatment effect; hence, it may also be considered a very conservative approach.

B12. The results of the multiple imputation approach give more consistent results between ESENSE1 and ESENSE2 and are more conservative; please explain why these results should not be considered as the base case.

The MMRM analysis was pre-specified as the primary analysis and is considered a robust methodology to analysis repeated measurements, while the multiple imputation (MI) method is considered a very conservative approach (see justification provided to question B11). The MI approach is particular conservative in case of differential withdrawal as the nalmefene group is penalised from both the overall withdrawal rate and the differential withdrawal rate. Thus MI approach is considered too conservative to be considered as the base case.

B13. Please clarify what is meant by observed cases in tables such as Table B46 (page 156).

The primary analysis for the co-primary efficacy variables was a mixed model repeated measures (MMRM) analysis using all available data measured over each month during the treatment period. The MMRM model used observed cases (OC)

B14. Please clarify whether the studies in Table B10 (page 91) were full intention to treat analyses, or whether these were modified intention to treat analyses.

The studies in Table B10 page 91 of the MS were modified intention to treat analyses. This modified ITT corresponds to all randomised patients excluding those who did not take the treatment or all IMP returned.

B15. Please provide further details (methodology, sample size and tabulated results) on the survey conducted by Lundbeck on the use of psychosocial interventions in England (page108).

The survey was undertaken by Lundbeck following discussion with the NICE STA Project Team at the Decision Problem meeting on 10th December 2013. It was felt at that meeting that it would be helpful to understand precisely which types of psychosocial intervention were being offered in clinical practice, to which patients and with what frequency. The survey was undertaken for this specific purpose.

Methodology

Lundbeck approached GP practices and specialist alcohol services in each of its 14 commercial regions across England. Respondents were asked the following three questions:

- Please describe the types of patients you currently treat for alcohol dependence;
- For a patient who is diagnosed with alcohol dependence but who does not have physical withdrawal symptoms or need immediate detoxification, please describe your current treatment options and rationale for each option;
- Which of the following types of psychosocial or psychological intervention do you use in your practice for the patients who do not require immediate detoxification? And approximately how many of these patients are offered each option?

Results

Responses were received from more than 20 primary care practices and specialist alcohol centres/ addiction clinics from across England (spanning 8 of the 14 commercial regions).

(i) Patients presenting

The survey responses revealed that the type of patient presenting with alcohol problems in primary care (Tier 2) is very varied, with most practices confirming that patients present " at all levels". This includes hazardous and harmful drinkers, as well as patients with other comorbid physical and/or mental conditions, 'high risk' drinkers, and alcohol-dependent patients across the severity spectrum.

Specialist clinics and services (Tier 3) tend to see patients who are referred on from primary care, as well as patients who self-refer straight into Tier 3.

Respondents used a variety of terms for categorising sub-groups of patients, including those noted above, but most respondents described their patients either in terms of units of alcohol consumed per week and/or in terms of an AUDIT score.

(ii) *Types of patients treated*

The survey responses confirmed that primary care practices treat patients at the mild end of the severity spectrum and there was a good degree of commonality in terms of describing ‘mild’ dependence. Generally speaking, these patients were not considered in need of referral to the local Community Alcohol Team or in need of detoxification.

A range of services exists beyond primary care, including third sector services (Turning Point, Addaction), Community Alcohol Teams and CRI. Typically, these specialist services are treating the following types of patient:

- Those consuming in excess of 140-150 units of alcohol a week (equivalent to a minimum 15-20 units per day); and/or
- High or very high-risk drinkers with an AUDIT score of 16 or above.

These patients tended to be categorised as having moderate-severe alcohol dependency.

In addition, specialist services would treat some patients with only mild or harmful alcohol misuse if that patient had complex needs, such as opiate addiction, comorbid physical health problems and/or a mental health condition.

(iii) Treatment options

The survey responses confirmed that ‘Brief Intervention’ is the mainstay of treatment in primary care. In most areas, this ‘Brief Intervention’ consists of brief advice, given by the GP or practice nurse, to cut down or abstain from drinking. In some areas, but not all, the Brief Intervention is supplemented by a variety of low-intensity offerings, including psychosocial support of an unspecified nature, group therapy, a physical health check and/or vitamin supplementation.

For any patient needing further intervention, or an intervention more intensive than a ‘Brief Intervention’ primary care would refer the patient to one or more of the specialist services.

Perhaps not surprisingly, a wider range of treatment options is available to most specialist services, but the intervention offered varies considerably on a patient-by-patient basis. According to the survey responses, even in the specialist centres, ‘Brief Intervention’ and “Extended Brief Intervention’ are routinely available for 80-100% of patients.

In terms of the types of psychosocial interventions currently mentioned in NICE Clinical Guideline 115, Cognitive Behavioural-Based Therapies (Standard CBT and/or coping skills) were available in 4 of the specialist centres surveyed, and might be offered to up to 20-30% of patients in that setting.

Other centres reported using a variety of more intensive interventions – behavioural therapies, behavioural self-control training, aversion therapy, counselling, cue exposure, behavioural and network therapy – but (with the one exception given below) in a minority of patients only (up to 10%).

Of the centres that were surveyed, respondent E offered the widest range of psychosocial interventions to patients.in the percentages listed below. An individual patient can be offered more than one type of intervention:

Intervention	Percentage of patients given it
Standard Cognitive Behaviour Therapy (CBT)	60%

Coping Skills	80%
Social Skills Training	10%
Relapse Prevention	80%
Cue Exposure	30%
Behavioural Self-Control Training	30%
Aversion Therapy	5%
Social Behaviour and Network Therapy	20%
Couples Therapy (including behavioural couples therapy and other variants of couples therapy)	5%
Psychoeducational and motivational techniques	100%
Extended brief intervention	75%
Motivational Enhancement Therapy	100%

The full survey results are presented in Appendix 5.

B16. Please provide further information (or justification) for not undertaking the methodological quality assessment of included studies in the systematic review of naltrexone and psychosocial interventions.

A quality assessment was undertaken, but was unfortunately omitted from the submission. We apologise for this omission. This information is provided in Appendix 6 (naltrexone) and Appendix 7 (psychosocial interventions) of this document.

B17. Please clarify if any attempt was made to seek clarification (including obtaining relevant data that was not reported in the published papers) from the authors of the included naltrexone and psychosocial intervention studies (Table B29; page 124).

We confirm that we have not contacted authors of the included naltrexone and psychosocial intervention studies for requesting potential additional unpublished data. This was having in mind our understanding that, for their evidence assessment, NICE favour the use of data that have been through peer-review process.

B18. Please clarify the methods of data synthesis in the systematic review of naltrexone and psychosocial interventions. In addition, please explain why the outcome data from the psychosocial intervention trials were not amenable to meta-analysis.

As noted in Section 6.7.3 of the MS (pages 113-123), the outcomes considered of relevance for the naltrexone and psychosocial intervention reviews were selected based on the EMA guideline recommendations regarding harm reduction studies such as nalmefene ones. The outcomes of relevance were thus in accordance with the primary ones from the nalmefene studies and included level of alcohol consumption, number of drinks/day, number of heavy drinking days, and percentage of heavy drinking days.

The systematic literature review on psychosocial intervention was an update of the one performed by the NICE CG 115, using the same search and review methodology. From

this review, it was not possible to perform an indirect meta-analysis with nalmefene in line with NICE recommendations for evidence synthesis for decision-making, mainly because there is no common treatment arm to be used in conjunction with the nalmefene clinical trials. Therefore, another simpler approach was chosen to estimate as far as possible the results from the psychosocial intervention studies reviewed comparatively with the results from the nalmefene studies. The absolute reduction of alcohol consumption was assessed independently for the arms in the included trials evaluating psychosocial interventions, and this was compared with the nalmefene study results for absolute reduction of drinking. Additionally, this question was considered by the Guideline Development Group (GDG) for NICE CG 115. The GDG was also unable to integrate the psychosocial intervention studies within its indirect meta-analysis with naltrexone and acamprosate. So, in NICE CG 115 the cost-effectiveness analysis used the placebo arm from naltrexone and acamprosate studies for modelling the psychosocial intervention arm, as we did.

B19. Please provide safety outcome, compliance and adherence data (including sample size) for each treatment arm of the ESENSE1, ESENSE2 and SENSE trials separately for the licensed population and the total population.

These data are presented in Appendix 8.

Section C: Clarification on cost-effectiveness data

C1. Please clarify whether the risks of serious events in the model are adjusted for mortality. For example, the probability of moving from very high risk on treatment to heart disease is 0.14% for males in the 1st year (cell i196 of Input summary General) whilst mortality risk is 0.03% (cell i276). Does that imply that overall risk was 0.17%, or should the non-fatal risk be 0.11%?

The risk of non-fatal harmful events in the model is not adjusted for mortality but incorporated as two separate and uncorrelated risks in the model. Thus, for example, the overall risk of fatal and non-fatal heart disease is 0.17%.

C2. Please clarify whether there is an error in the model regarding mortality rates from people progressing from initial serious event. For example cell AK72 in the Markov Nalmefene sheet formula currently reads

"=AJ71+AK71*(1-VLOOKUP(ISG!$O$17,'GP Mortality'!$F$38:$I$120,4,FALSE))" whereas we suspect it should read "=(AJ71+AK71)*(1-VLOOKUP(ISG!$O$17,'GP Mortality'!$F$38:$I$120,4,FALSE))

If this formula is incorrect, please amend the model where required to ensure internal validity.

This is a good observation and we agree that our choice of modelling the general mortality for patients who have experienced a serious event could have been done as you suggest. However, we specifically modelled these patients not to experience death due to all causes the same month as their first month when acquiring the event. The reason for this was to minimise risk of double counting the events patients can experience (harmful events, harmful events deaths, and all-cause mortality). We have investigated the impact on varying our method with the one proposed, and it has a minor impact on the result. The change is to favour the strategy of nalmefene + psychosocial intervention even more

compared to psychosocial intervention alone (because fewer events are experienced by the nalmefene patients).

C3. Please clarify why a half-cycle correction has not been undertaken.

Applying half-cycle correction could have been relevant in this model. However there are reasons not to considering when some methodological publications and some particularities of our model methodology. These are as follows:

1. Our model has a short cycle length (1 month) for the first year, and the comparative effect between cohorts seen during the first year is driving the cost-effectiveness conclusion of the analysis. As reported by Sonnenberg & Beck (1993)*, a 1-month cycle length is minimal compared to the relative to average survival, and this lead to believe to a negligible effect of half cycle correction in our case.

2. As shown in by Naimark et al (2013)**, half cycle correction is believed to lead to a too large correction when a much larger proportion of subjects still inhabit non-absorbing states during the model time horizon, which is the case in the current model with a minimal proportion of patients captured by an absorbing state over the model 5-year time horizon.

* Sonnenberg, F. A., & Beck, J. R. (1993). MARKOV MODELS IN MEDICAL DECISION MAKING :A PRACTICAL GUIDE Markov Models in Medical Decision Making : A Practical Guide.

** Naimark, D. M. J., Kabboul, N. N., & Krahn, M. D. (2013). The half-cycle correction revisited: redemption of a kludge. Medical decision making : an international journal of the Society for Medical Decision Making, 33(7), 961–70. doi:10.1177/0272989X13501558.

C4. Please clarify why utilities for serious events are assumed invariant of time.

The utilities for serious events were taken from the Sheffield model; and were originally collected by the Cardiff & Vale NHS Hospital Trust serving: patients discharged from hospital were requested to complete an EQ-5D questionnaire 6 weeks after their discharge.

The EQ-5D data were collected 6 weeks post hospital discharge. Considering that the EQ-5D has no re-call period (assess health-related quality of life as for today), we may believe that this value kept stable for a certain time in the model would represent an appropriate average for this certain period of time. Nevertheless, we agree that we could have been assumed some utility variation. However, we would suggest that this would have created uncertainty in the cost-effectiveness analysis considering the lack of data for informing this variation. In addition, we are not aware of a validated methodological approach that would have allowed this.

Nevertheless, considering the incidence of serious events being relatively low, it would not have had any impact on the conclusion of the analysis. To demonstrate this, we have removed the modelling option of the incidence of all alcohol-attributable harmful events (morbidity and mortality), and this lead to nalmefene + psychosocial intervention still dominating psychosocial intervention alone as per the base-case analysis.

C5. Please clarify why the very high risk utility is used for the very high/high risk group and the abstinence utility for the low/abstinent group. Please also clarify the impact on the results where the alternative assumption is used.

In the three nalmefene clinical trials, Health-Related Quality of Life (HRQoL) was measured using EQ-5D at baseline, 3 months and 6 months, and additionally at 12 months for SENSE. Table 5 details the utility scores per drinking health state per treatment arm as estimated from the nalmefene clinical trials. Table 6 details utility scores combining the nalmefene and placebo treatment arms, as used for the base case analysis, and breaking down high & very high drinking levels, and low drinking level and abstinence.

Table 5. Mean utility score per drinking risk level per treatment arm pooling the 3 nalmefene clinical trials and all time-point observations

Drinking risk level	Nalmefene		Placebo	
	N Obs	Utility score	N Obs	Utility score
Very high	337	[redacted]	339	[redacted]
High	332	[redacted]	282	[redacted]
Medium	159	[redacted]	126	[redacted]
Low	331	[redacted]	158	[redacted]
Abstinence	67	[redacted]	36	[redacted]

Table 6. Mean utility score per drinking risk level combining trials treatment arms and pooling the 3 nalmefene clinical trials and all time-point observations

Drinking risk level	Current model	Requested breakdown
Very high		[redacted]
High	0.79	[redacted]
Medium	0.82	[redacted]
Low		[redacted]
Abstinence	0.86	[redacted]

As we can see in Table 5 and Table 6, the EQ-5D questionnaire may not be highly sensitive to outcome changes in alcohol dependence, as it was suggested by Luquiens et al 2012***. There could be insufficient correlation between changes in drinking behaviour and alcohol consumption with patient perceived impact on health status using this measure.

To optimise the capture of changes in HRQoL, in the base case, we estimated the mean QALY difference between the two treatment strategies during the first year 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 three months from baseline to one 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. For the long-term phase of the model, we derived utility weights for drinking health state. The breakdown utility scores shown in the right column of Table 6 have been used in a scenario analysis and this gives slightly higher incremental QALYs favouring nalmefene than the base case analysis (Table 7).

Table 7. Analysis varying the utility score per drinking risk level

Scenario	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
	NMF + PI	PI alone	NMF + PI	PI alone			
Base case	£4,445	£4,842	3.624	3.553	-£397	0.071	Nalmefene dominates
Using the breakdown utility scores	£4,803	£5,240	3,636	3,554	-£397	0,082	Nalmefene dominates

*** Luquiens A RM, Falissard B, Aubin HJ. Quality of life among alcohol-dependent patients: how satisfactory are the available instruments? A systematic review. Drug Alcohol Depend. 2012;125(3):192-202.

C6. Please clarify how drop-outs were handled within the utility calculations.

For the main treatment year of the model (first year) comparing nalmefene + psychosocial intervention versus psychosocial intervention alone and based on the nalmefene clinical trials, the QALY difference between treatment arm (to which was applied QALY decrements from the incidence of alcohol-attributable harmful events), was estimated using the area between the curves of pooled adjusted mean utility scores for nalmefene and placebo patients from the trials, as described in C5. This was performed using observed cases, without the application of an imputation method for missing data.

C7. Please clarify whether having a non-fatal serious event (such as heart disease) is associated with mortality risk. Cell G102 on the 'Data Store' Sheet implies no mortality.

This is correct to say that there is no risk of mortality incorporated in the model and applied to the patients experiencing a serious harmful event; these patients are moved to an absorbing state. The model has been developed like this as there is uncertainty about continued drink patterns after a serious event and conditional probabilities of experiencing further harmful events after the initial one. To be conservative, we chose not to model this specifically in the current version of the model.

C8. Please clarify why mortality rates associated with chronic events are diminished by underlying general population mortality. For example, cell AT71 in the Markov Nalmefene sheet, the risks of mortality from events are multiplied by the survival rate. It is expected that the risks reported are not conditional on survival. If this is an error further amendments would be needed to maintain internal validity.

Mortality rates associated with chronic events are diminished by underlying general population mortality in the model because it is assumed that all-cause mortality would take priority over dying from alcohol-related events during the year.

C9. Please clarify why it is assumed that the summed probability of non-fatal lower respiratory infections, transport injuries and other injuries are not assumed mutually exclusive from the summed totals of heart disease, ischaemic stroke, haemorrhagic stroke, liver cirrhosis and pancreatitis and fatal lower respiratory infections, transport injuries and other injuries, yet non-fatal heart disease, ischaemic stroke, haemorrhagic stroke, liver cirrhosis and pancreatitis is assumed mutually exclusive from fatal heart disease, ischaemic stroke, haemorrhagic stroke,

liver cirrhosis and pancreatic lower respiratory infections, transport injuries and other injuries events.

Non-fatal short term events are not mutually exclusive from the summed totals of all events because these patients are considered to continue to drink while having a non-fatal short term harmful event. Thus, patients continue to have a risk of experiencing other harmful events considered in the model. However, patients experiencing a non-fatal serious harmful event are removed from the portion of the model where patients are drinking and continue in a post-event state (absorbing state) for the rest of the model's timeframe. This is considering that the seriousness of these diseases is assumed to preclude continued drinking. Thus, serious harmful events are assumed mutually exclusive from another alcohol-related harmful event. The reason for modelling serious harmful events in this manner is to take a conservative approach avoiding making assumptions about continued drink patterns after a serious event and conditional probabilities of experiencing further serious harmful events after the initial one. As there is a higher drinking level, and thus incidence of serious harmful events, for patients treated with psychosocial intervention alone compared to nalmefene + psychosocial intervention, this is also seen as a conservative assumption.

Section D: Textual clarifications and additional points

D1. Please confirm whether the data are correct in Figure B4 (page 89) for the nalmefene + PI group (for example the number of withdrawals plus the number of patients who completed the study does not equate to the number of patients treated).

Unfortunately, the number given of patients who completed the study for the nalmefene + PI group was incorrect. The correct number of patients who completed the study is 77 patients.

D2. Please clarify and explain the apparent discrepancies between the manufacturer's submission (Table B13; page 95) and the Summary of Product Characteristics (Table 2) with respect to the TAC R70 (≥ 70% reduction in total alcohol consumption) value.

In the MS, the data were reported based on the pre-specified mixed model repeated measures (MMRM) analysis using all available data measured over each month during the treatment period, whereas reported values in the Summary of Product Characteristics are based on non-response imputation. MMRM has been accepted by the regulatory authorities.

D3. Please comment on a rapid response published in the BMJ by Alain Braillon (available at http://www.bmj.com/content/348/bmj.g1531?tab=responses) which states that "in 1998 Contral Pharma Ltd tried to develop nalmefene for alcohol related problems but in 2003 nalmefene didn't succeed to meet phase III clinical end points statistically significantly. These data must be disclosed too". If appropriate, and available please provide the relevant data from this trial, or state the reason for not doing so.

The main authors of the nalmefene ESENSE1, ESENSE 2 and SENSE studies have themselves commented recently on Dr Braillon's letter, and concluded that he makes

“strong statements” on “(even) less well-informed grounds”. Their response can be found at: (http://www.bmj.com/content/348/bmj.g2017?tab=responses).

Dr. Braillon mentions that in 1998 Contral Pharma started development work on nalmefene in alcohol use-disorders, and in 2001 they launched two studies, which are most likely referred to in his response. These two studies are included in the MS as CPH-101-701 and CPH-101-0801 (page 277, table 10). Whereas the later one was published in 2007 (Karhuvaara et al., 2007), and robustly met primary as well as several secondary endpoints, the smaller UK study has not been published in a peer-reviewed journal and did not meet primary endpoints. However, both studies have limitations in their relevance to the scope of this submission, as outlined in table 10 on page 277 of the MS.

Furthermore, it is important to note that Contral Pharma merged with Biotie and the development of nalmefene thus became a Biotie programme. As such, the full programme (including the Contral Pharma initiated studies), consisting of five studies, has been included in the MS as Biotie-sponsored studies (page 277 of the MS, Table 10-1, Biotie-sponsored studies evaluating nalmefene in alcohol-use disorders). Lundbeck has not been involved in the Biotie programme and does not have responsibility for the study conductance. Dr. Braillon suggested that experience prior to the Lundbeck nalmefene phase 3 programme were not taken into account by the EMA decision to grant license for nalmefene. However, the full Biotie programme has been disclosed to the EMA, and indeed an overview of all five studies have become publically available in the Committee for Medicinal Product for Human Use Assessment Report on Selincro (EMA/78844/2013).

Clarification Appendices

Appendix 1. Rescreening of Non-English Articles Excluded at Level 1 Screening, Pharmacological Interventions Systematic Literature Review

No.	Reference	Reason for exclusion upon rescreening
1	[Deficits in preventing recurrence in alcoholic patients. Withdrawal--and immediately back to the bottle]. MMW Fortschr Med 2003 Jan 16;145(1-2):55.	Non-systematic review/comment article
2	[Preventing recurrence after alcohol withdrawal treatment with drugs. Reducing the drive to drink]. MMW Fortschr Med 2003 May 8;145(19):56.	Non-systematic review/comment article
3	[Update on current care guidelines: treatment of alcohol abuse]. Duodecim 2010;126(11):1353-4.	Non-systematic review
4	Batel P, Balester-Mouret S. [Maintaining abstinence after alcohol detoxification]. Rev Prat 2006 May 31;56(10):1100-6.	Detoxified patients
5	Berglund M, Balldin J, Bendtsen P, Borg S, Franck J, Gustafsson L, et al. [Pharmacological treatment of alcohol dependence. Acamprosate and naltrexone offer new approach]. Lakartidningen 1997 Jul 23;94(30-31):2645-8.	Non-systematic review/comment article
6	Brambilla R, Vigna-Taglianti F, Avanzi G, Faggiano F, Leone M. [Gamma-hydroxybutyrate (GHB) for mid/long term treatment of alcohol dependence: a systematic review]. Riv Psichiatr 2012 Jul;47(4):269-80.	Gamma-hydroxybutyrate
7	Brewer C. El disulfiram supervisado es mbs eficaz en alcoholismo que la naltrexona o el acamprosato e incluso la psicoterapia: C£mo funciona y por quq es importante. Adicciones 2005;17(4):285-96.	Non-systematic review
8	Castro LA, Baltieri DA. [The pharmacologic treatment of the alcohol dependence]. Rev Bras Psiquiatr 2004 May;26 Suppl 1:S43-S46.	Non-systematic review
9	Diehl A, Mann K. [Pharmacological relapse prevention in alcohol and tobacco dependence]. Internist (Berl) 2007 Jan;48(1):79-8.	Non-systematic review
10	Florez G, Saiz PA, Garcia-Portilla P, Alvarez S, Nogueiras L, Bobes J. [Amisulpride for the treatment of alcohol dependence]. Adicciones 2011;23(2):149-56.	Detoxified patients
11	Golovko SI, Zefirov SI, Golovko AI, Shpilenia LS, Nekrasov I. [Acamprosate--a novel treatment for alcoholism]. Eksp Klin Farmakol 2000 May;63(3):70-3.	Non-systematic review
12	Gual SA. [Naltrexone in the treatment of alcoholism. Clinical evolution, safety and efficacy in a sample of 198 patients]. Med Clin (Barc) 2001 Apr 21;116(14):526-32.	Patients submitted to detoxification, goal of abstinence
13	Guardia SJ, Segura GL, Gonzalvo CB, Trujols AJ, Tejero PA, Suarez GA, et al. [Validation study of the Multidimensional Alcohol Craving Scale (MACS)]. Med Clin (Barc) 2004 Jul 10;123(6):211-6.	PRO validity study
14	Ladewig D, Knecht T, Leher P, Fendl A. [Acamprosate--a stabilizing factor in long-term withdrawal of alcoholic patients]. Ther Umsch 1993 Mar;50(3):182-8.	Alcohol withdrawal
15	Lopez-Ibor Alino JJ, Perez de los Cobos JC, Ochoa E, Hernandez HM. [Maintenance treatment for opiate dependence at a naltrexone clinic]. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1990 Sep;18(5):296-305.	Opiate dependence
16	Mutschler J, Diehl A, Vollmert C, Herre H, Mann K, Kiefer F. [Recent results in relaps prevention of alcoholism with Disulfiram]. Neuropsychiatr 2008;22(4):243-51.	Non-systematic review
17	Mutschler J, Kobiella A, Grosshans M, Kiefer F. [Impact of functional social support for abstinence after inpatient detoxification]. Neuropsychiatr 2010;24(2):118-24.	Detoxified patients
18	Nalpas B, Dabadie H, Parot P, Paccalin J. [Acamprosate. From pharmacology to therapeutics]. Encephale 1990 May;16(3):175-9.	Non-systematic review

No.	Reference	Reason for exclusion upon rescreening
19	Ochoa ME, Arias HF, Torres Hernandez MA. [Alcohol dependence treatment with naltrexone: safety assessment. Observation study group of alcoholic dependence]. Actas Esp Psiquiatr 2000 May;28(3):161-8.	Non-controlled/non-comparative study
20	Petrov I, Krogh J, Nordentoft M. [Meta-analysis of pharmacological therapy with acamprosate, naltrexone, and disulfiram--a systematic review]. Ugeskr Laeger 2011 Nov 28;173(48):3103-9.	Systematic review/meta-analysis
21	Ponce G, Sanchez-Garcia J, Rubio G, Rodriguez-Jimenez R, Jimenez-Arriero MA, Palomo T. [Efficacy of naltrexone in the treatment of alcohol dependence disorder in women]. Actas Esp Psiquiatr 2005 Jan;33(1):13-8.	Abstinent population
22	Poser W, Ehrenreich H. [Naltrexone--prevention of recurrence in narcotic dependence and in alcoholism]. Internist (Berl) 1996 Oct;37(10):1061-7.	Narcotic dependence
23	Roussaux JP, Hers D, Ferauge M. [Does acamprosate diminish the appetite for alcohol in weaned alcoholics?]. J Pharm Belg 1996 Mar;51(2):65-8.	Weaned alcoholics
24	Rubio VG, Espi MF, Sanchis FM, Bravo Garcia De Laguna JL. [Naltrexone use in the treatment of alcoholism in Spain]. Rev Clin Esp 2002 Aug;202(8):435-9.	Prescribing patterns
25	Rueff B. [Evaluation of drug treatment of primary alcoholism]. Rev Prat 1999 Feb 15;49(4):400-2.	Non-systematic review
26	Rychlik R, Paschen B, Kirchhoff D, Daniel D, Pfeil T, Kilburg A. [Adjuvant drug treatment of alcoholism with acamprosate: between sectoral budgets and disease management]. Dtsch Med Wochenschr 2001 Aug 17;126(33):899-904.	Detoxified patients
27	Salaspuro M. [Drug therapy of alcohol dependence--a critical review]. Duodecim 2003;119(24):2503-7.	Non-systematic review
28	Sass H, Mann K, Soyka M. [Relapse prophylaxis medicinally supported by Acamprosate in alcohol dependent patients - Results of a double-blind, randomised, placebo-controlled study]. Sucht 1996;42:316-22.	Relapse prevention, implies abstinent patients
29	Schmitt-Honl B. [Alcohol dependence. Behavior therapy is effective with naltrexone]. Med Monatsschr Pharm 2006 Oct;29(10):380-1.	Non-systematic review
30	Sivolap I, Savchenkov VA. [Preventive therapy of opiate addiction with naltrexone]. Zh Nevrol Psikhiatr Im S S Korsakova 1998;98(11):22-5.	Opiate addiction
31	Smolka MN, Kiefer F, Mann K. [Advances in the treatment of alcohol dependence: pharmacological relapse prevention]. MMW Fortschr Med 2003 Oct 9;145 Suppl 3:65-9.	Non-systematic review
32	Smolka MN, Kiefer F, Mann K. [Psychosocial treatment plus drug prophylaxis. Fewer recurrences after alcohol withdrawal]. MMW Fortschr Med 2003 Sep 4;145(35-36):45.	Patients who have withdrawn from alcohol
33	Soyka M, Kotter G, Preuss U, Schutz C. [Pharmacotherapy of alcoholism]. Med Monatsschr Pharm 1996 Dec;19(12):359-64.	Non-systematic review
34	Soyka M, Zieglgansberger W. [Prevention of recurrent alcoholism with acamprosate. Neurobiological principles and clinical results]. Internist (Berl) 1999 Mar;40(3):330-6.	Not intervention of interest (acamprosate)
35	Wobrock T, D'Amelio R, Falkai P. [Pharmacotherapy of schizophrenia and comorbid substance use disorder. A systematic review]. Nervenarzt 2008 Jan;79(1):17-2, 24.	Schizophrenia

a This article was excluded at level 1 as a non-English language article. Upon rescreening, it was excluded at level 2 for being a systematic review and meta-analysis.

Appendix 2. Rescreening of Non-English Articles Excluded at Level 2 Screening - Pharmacological Interventions Systematic Literature Review

No.	Reference	Reason for exclusion
1	Arbaizar B, Dierssen-Sotos T, Gomez-Acebo I, Llorca J. Topiramato en el tratamiento de la dependencia etÆlica: Un metaanblisis. Actas Espa±olas de PsiquiatrÆa 2010;38(1):8-12.	Meta-analysis
2	Banzato CEM, Loper AD, de Azevedo RCS. Naltrexona na dependWncia de blcool: Ensaio clÆnico aberto. Jornal Brasileiro de Psiquiatria 2004;53(2):134-8.	Non-randomized study
3	Bijl D. Acamprosate for alcohol dependence: A meta-analysis. Geneesmiddelenbulletin 2011;45(3):31-2.	Meta-analysis
4	Castro LA, Laranjeira R. A double blind, randomized and placebo-controlled clinical trial with naltrexone and brief intervention in outpatient treatment of alcohol dependence. Jornal Brasileiro de Psiquiatria 2009;58(2):79-85.	Abstinence period of 5 to 30 days prior to entry
5	Castro LA, Laranjeira R. Ensaio clínico duplo-cego randomizado e placebocontrolado com naltrexona e intervenção breve no tratamento ambulatorial da dependência de álcool.. Jornal Brasileiro de Psiquiatria 2009;58(2):79-85.	Duplicate
6	Fl£rez G, Saiz PA, GarcÆa-Portilla P, -lvarez S, Nogueiras L, Bobes J. Amisulpride en el tratamiento de la dependencia alcoh£lica. Adicciones 2011;23(2):149-56.	Detoxified patients
7	Gammeter R. Connaissances actuelles sur l'efficacitq de la naltrexone en alcoologie. Alcoologie et Addictologie 2005;27(3):227-32.	Systematic review/meta-analysis
8	Huang X, Huang X, Peng H, Mai G. Placebo-controlled trial of naltrexone in outpatient treatment of alcohol dependence. Chinese Mental Health Journal 2002;16:302-3.	Chinese population of patients who received a different dose of naltrexone than the one approved for alcohol dependence in Europe
9	INTEGRAL study: Acamprosate and short intervention for alcohol withdrawal. Deutsche Apotheker Zeitung 1998;138(36):28-30.	Alcohol withdrawal treatment
10	Izquierdo M, Rodriguez-Martos A, Llopis J, Ca±uelo B, Guigou G, Izquierdo J, et al. Uso de naltrexona en la deshabituaci£ n de pacientes con dependencia de alcohol en el estado espa±ol. Adicciones 2002;14(3):327-35.	Duplicate
11	Izquierdo M, Rodriguez-Martos A, Llopis J, Canuelo B, Guigou G, Izquierdo J, et al. Use of naltrexone in the rehabilitation of Spanish alcohol dependent patients. Adicciones 2002;14(3):327-35.	Non-randomized observational study
12	Kiefer F, Jahn H, Holzbach R, Briken P, Stracke R, Wiedemann KI. Die NALCAM-Studie: Wirksamkeit, VertrSglichkeit, Outcome. Sucht: Zeitschrift fnr Wissenschaft und Praxis 2003;49(6):342-51.	Detoxified patients
13	Kopczynska E, Lampka M, Torlinski L, Ziolkowski M. The level of 8-iso-prostaglandin F2a, 4-hydroxynonenal and malondialdehyde in alcohol dependent men during combined therapy. Psychiatria Polska 2002;36(2):293-302.	Not outcome of interest (lipid peroxidation)
14	Ochoa Mangado E, Arias Horcajadas F, Torres Hernbndez MA. Evaluaci£n de la seguridad del tratamiento con naltrexona en la dependencia del alcohol. Actas Espa±olas de PsiquiatrÆa 2000;28(3):161-8.	Duplicate
15	ovb D, Ignatovi? M, Jankovi?-Gaji? J. Acamprosbt v ambulantnej lie?be pacientov so syndr£mom zbvislosti na alkohole. ?eskb a Slovenskb Psychiatrie 2002;98(7):388-92.	Abstinent patients
16	Ponce G, Sbnchez-GarcÆa J, Rubio G, RodrÆguez-Jimqnez R, Jimqnez-Arriero M, Palomo T. Eficacia de la naltrexona en el tratamiento de mujeres con trastorno por dependencia del alcohol. Actas Espa±olas de PsiquiatrÆa 2005;33(1):13-8.	Duplicate

No.	Reference	Reason for exclusion
17	Sass H, Mann K, Soyka M. Drug support for prevention of relapse in alcoholic patients with acamprosate: Results of a double blind, randomized, placebo controlled study. Sucht 1996;42(5):316-22.	Relapse prevention suggests abstinent patients
18	ska E, Lampka M, ski L, kowski M. Ste?enie 8-izo-prostaglandyny F?? oraz 4-hydroksynonenalu i dialdehydu malonowego u os£b uzale?nionych od alkoholu w trakcie kompleksowej terapii odwykowej. Psychiatria Polska 2002;36(2):293-302.	Duplicate

Appendix 3. Pharmacological Interventions Systematic Literature Review: Full-Text Articles Excluded at Level 2 Screening and Reasons for Exclusion

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
1	Abstracts from the 2007 Amersa National Meeting. Substance Abuse 2009;30(2):191-212.	Abstracts book
2	Ades J, Lejoyeux M. Clinical evaluation of acamprosate to reduce alcohol intake. Alcohol Alcohol Suppl 1993;2:275-8.	Non-systematic review
3	Agosti V, Nunes EV, O'Shea D. Do manualized psychosocial interventions help reduce relapse among alcohol-dependent adults treated with naltrexone or placebo? A meta-analysis (Provisional abstract). Database of Abstracts of Reviews of Effects 2012;501-7.	Meta-analysis; duplicate
4	Agosti V, Nunes EV, O'Shea D. Do manualized psychosocial interventions help reduce relapse among alcohol-dependent adults treated with naltrexone or placebo? A meta-analysis. Am J Addict 2012 Nov;21(6):501-7.	Meta-analysis
5	Agosti V. The efficacy of controlled trials of alcohol misuse treatments in maintaining abstinence: a meta-analysis (Structured abstract). International Journal of the Addictions 1994;29:759-69.	Meta-analysis; duplicate
6	Agosti V. The efficacy of controlled trials of alcohol misuse treatments in maintaining abstinence: a meta-analysis. Int J Addict 1994 Apr;29(6):759-69.	Meta-analysis
7	Ahmadi J, Babaeebeigi M, Maany I, Porter J, Mohagheghzadeh M, Ahmadi N, et al. Naltrexone for alcohol-dependent patients. Ir J Med Sci 2004 Jan;173(1):34-7.	Sober at entry
8	Ait-Daoud N, Johnson BA, Prihoda TJ, Hargita ID. Combining ondansetron and naltrexone reduces craving among biologically predisposed alcoholics: preliminary clinical evidence. Psychopharmacology (Berl) 2001 Feb;154(1):23-7.	Predictor/prognostic study
9	Alho H. Disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. European Psychiatry 2009;24:S298.	Level of alcohol conumption not stated; abstract only
10	Ansoms C, Deckers F, Lehert P, Pelc I, Potgieter A. An open study with acamprosate in Belgium and Luxemburg: results on sociodemographics, supportive treatment and outcome. Eur Addict Res 2000 Sep;6(3):132-40.	First two week of study abstinent
11	Anton RF, Drobes DJ, Voronin K, Durazo-Avizu R, Moak D. Naltrexone effects on alcohol consumption in a clinical laboratory paradigm: temporal effects of drinking. Psychopharmacology (Berl) 2004 Apr;173(1-2):32-40.	Patients were required to abstain on day 6, alcohol withdrawal is outcome
12	Anton RF, Moak DH, Latham P, Waid LR, Myrick H, Voronin K, et al. Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence. J Clin Psychopharmacol 2005 Aug;25(4):349-57.	Sober at entry
13	Anton RF, Moak DH, Latham PK, Waid LR, Malcolm RJ, Dias JK, et al. Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. J Clin Psychopharmacol 2001 Feb;21(1):72-7.	Level of drinking not detailed

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
14	Anton RF, Moak DH, Waid LR, Latham PK, Dias JK. Naltrexone plus cognitive-behavior therapy for alcoholism. 152nd Annual Meeting of the American Psychiatric Association Washington DC , USA 15 20th May , 1999 1999.	Level of alcohol consumption not detailed; abstract only
15	Anton RF, Myrick H, Latham PK, Randall PK, Baros AM, Wright TM, et al. Alcoholwithdrawal syndrome and relapse: Role of gabapentin treatment. Alcoholism: Clinical and Experimental Research 2013;37:279A.	Alcohol withdrawal syndrome
16	Anton RF, Myrick H, Wright TM, Latham PK, Baros AM, Waid LR, et al. Gabapentin combined with naltrexone for the treatment of alcohol dependence. Am J Psychiatry 2011 Jul;168(7):709-17.	Abstinent for 4 days before randomisation
17	Arbaizar B, Diersen-Sotos T, Gomez-Acebo I, Llorca J. Topiramate in the treatment of alcohol dependence: a meta-analysis. Actas Esp Psiquiatr 2010 Jan;38(1):8-12.	Meta-analysis
18	Arbaizar B, Dierssen-Sotos T, Gomez-Acebo I, Llorca J. Topiramato en el tratamiento de la dependencia etÆlica: Un metaanblisis. Actas Espa±olas de PsiquiatrÆa 2010;38(1):8-12.	Non-English language
19	Armeli S, Feinn R, Tennen H, Kranzler HR. The effects of naltrexone on alcohol consumption and affect reactivity to daily interpersonal events among heavy drinkers. Exp Clin Psychopharmacol 2006 May;14(2):199-208.	Correlation/predictor study
20	Attilia F, Rotondo C, Attilia ML, Tavoletti R, Ceccanti M. Efficacy and tolerability of acamprosate vs. naltrexone in patients with alcohol dependence. Preliminary study. Digestive and Liver Disease 2012;44:S184.	Goal of abstinence
21	Aubin HJ, Daeppen JB. Emerging pharmacotherapies for alcohol dependence: A systematic review focusing on reduction in consumption. Drug Alcohol Depend 2013 Jun 6.	Systematic review
22	Balldin J, Berglund M, Borg S, Mansson M, Bendtsen P, Franck J, et al. A 6-month controlled naltrexone study: combined effect with cognitive behavioral therapy in outpatient treatment of alcohol dependence. Alcohol Clin Exp Res 2003 Jul;27(7):1142-9.	Not allowed to be drinking at baseline and for at least 1 week beforehand
23	Balldin J, Berglund M, Borg S, Mansson M. THE SWEDISH NALTREXONE STUDY, PRESENT RESULTS. 9th Congress of the Association of European Psychiatrists Copenhagen, Denmark 20 24th September 1998 1998.	Level of alcohol consumption not detailed; abstract only
24	Baltieri DA, Daro FR, Ribeiro PL, De Andrade AG. Comparing topiramate with naltrexone in the treatment of alcohol dependence. Addiction 2008 Dec;103(12):2035-44.	Detoxified patients
25	Banzato CEM, Loper AD, de Azevedo RCS. Naltrexona na dependWncia de blcool: Ensaio clÆnico aberto. Jornal Brasileiro de Psiquiatria 2004;53(2):134-8.	Non-English language
26	Batel P. The treatment of alcoholism in France. Drug Alcohol Depend 1995 Sep;39 Suppl 1:S15-S21.	Meta-analysis
27	Berger L, Brondino M, Fisher M, Gwyther R, Garbutt JC. Managing alcohol dependence in a primary care setting: the role of treatmentgoal. Alcoholism: Clinical and Experimental Research 2013;37:294A.	Abstinent at entry
28	Berger L, Fisher M, Brondino M, Bohn M, Gwyther R, Longo L, et al. Efficacy of acamprosate for alcohol dependence in a family medicine setting in the United States: a randomized, double-blind, placebo-controlled study. Alcohol Clin Exp Res 2013 Apr;37(4):668-74.	Abstinent prior to randomisation

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
29	Berger L, Zweben A, Brondino M. The impact of supportive significant others on patient alcohol outcomes in a combined medication and behavioral alcohol treatment study. Alcoholism: Clinical and Experimental Research 2009;33:284A.	COMBINE study, patients detoxified on entry
30	Besson J, Aeby F, Kasas A, Lehert P, Potgieter A. Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study. Alcohol Clin Exp Res 1998 May;22(3):573-9.	Abstinent at entry
31	Bijl D. Acamprosate for alcohol dependence: A meta-analysis. Geneesmiddelenbulletin 2011;45(3):31-2.	Non-English language
32	Boothby LA, Doering PL. Acamprosate for the treatment of alcohol dependence. Clin Ther 2005 Jun;27(6):695-714.	Systematic review
33	Bouza C, Angeles M, Munoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review (Provisional abstract). Addiction 2004;99:811-28.	Systematic review; duplicate
34	Bouza C, Angeles M, Munoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. Addiction 2004 Jul;99(7):811-28.	Systematic review
35	Bouza C, Angeles M, Munoz A, Amate JM. Erratum: Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: A systematic review (Addiction (2004) 99 (811-828)). Addiction 2005;100(4):573.	Erratum for author name
36	Brasser SM, McCaul ME, Houtsmuller EJ. Alcohol effects during acamprosate treatment: a dose-response study in humans. Alcohol Clin Exp Res 2004 Jul;28(7):1074-83.	Not alcohol-dependent
37	Cada DJ, Levien T, Baker DE. Acamprosate calcium delayed-release tablets. Hospital Pharmacy 2004;39(12):1177-85.	Non-systematic review
38	Carter AC, Miranda R, Gwaltney C, Tidey J, Rohsenow DJ, Swift R, et al. Naltrexone's impact on alcohol expectancies in heavy drinkers. Alcoholism: Clinical and Experimental Research 2010;34(6):177A.	Heavy drinkers
39	Castro LA, Laranjeira R. A double blind, randomized and placebo-controlled clinical trial with naltrexone and brief intervention in outpatient treatment of alcohol dependence. Jornal Brasileiro de Psiquiatria 2009;58(2):79-85.	Non-English language
40	Castro LA, Laranjeira R. Ensaio clÆnico duplo-cego randomizado e placebo-controlado com naltrexona e interventpo breve notratamento ambulatorial da dependWncia de blcool. Jornal Brasileiro de Psiquiatria 2009;58(2):79-85.	Non-English language
41	Chick J, Anton R, Checinski K, Croop R, Drummond DC, Farmer R, et al. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol 2000 Nov;35(6):587-93.	Abstinent at entry
42	Ciraulo DA, Dong Q, Silverman BL, Gastfriend DR, Pettinati HM. Early treatment response in alcohol dependence with extended-release naltrexone. J Clin Psychiatry 2008 Feb;69(2):190-5.	Injectable naltrexone (not available in Europe)
43	Cisler RA, Silverman BL, Gromov I, Gastfriend DR. Impact of treatment with intramuscular, injectable, extended-release naltrexone on counseling and support group participation in patients with alcohol dependence. J Addict Med 2010 Sep;4(3):181-5.	Injectable naltrexone (not available in Europe)

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
44	Colagiuri B, Morley K, Boakes R, Haber P. Expectancy in double-blind placebo-controlled trials: an example from alcohol dependence. Psychother Psychosom 2009;78(3):167-71.	Abstinent at entry
45	Cutler RB. Abatement of craving in recovering alcoholics: A descriptive analysis. Addiction Research & Theory 2005;13(2):111-27.	Pharmacotherapy alone
46	Dahl H, Hammarberg A, Franck J, Helander A. Urinary ethyl glucuronide and ethyl sulfate testing for recent drinking in alcohol-dependent outpatients treated with acamprosate or placebo. Alcohol Alcohol 2011 Sep;46(5):553-7.	Pharmacotherapy alone
47	Davidson D, Gulliver SB, Longabaugh R, Wirtz PW, Swift R. Building better cognitive-behavioral therapy: is broad-spectrum treatment more effective than motivational-enhancement therapy for alcohol-dependent patients treated with naltrexone? J Stud Alcohol Drugs 2007 Mar;68(2):238-47.	Abstinent on entry
48	Davidson D, Palfai T, Bird C, Swift R. Effects of naltrexone on alcohol self-administration in heavy drinkers. Alcohol Clin Exp Res 1999 Feb;23(2):195-203.	Heavy beer drinkers
49	Davidson D, Saha C, Scifres S, Fyffe J, O'Connor S, Selzer C. Naltrexone and brief counseling to reduce heavy drinking in hazardous drinkers. Addict Behav 2004 Aug;29(6):1253-8.	Non-alcohol dependent
50	Davidson D, Wirtz PW, Gulliver SB, Longabaugh R. Naltrexone's suppressant effects on drinking are limited to the first 3 months of treatment. Psychopharmacology (Berl) 2007 Sep;194(1):1-10.	Abstinent on entry
51	de SA, de SA. A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. Alcohol Alcohol 2004 Nov;39(6):528-31.	Undergoing detoxification on entry
52	de SA, de SA. An open randomized study comparing disulfiram and acamprosate in the treatment of alcohol dependence. Alcohol Alcohol 2005 Nov;40(6):545-8.	Undergoing detoxification on entry
53	De Wildt WA, Schippers GM, van den Brink W, Potgieter AS, Deckers F, Bets D. Does psychosocial treatment enhance the efficacy of acamprosate in patients with alcohol problems? Alcohol Alcohol 2002 Jul;37(4):375-82.	Abstinent on entry
54	Del Re AC, Maisel N, Blodgett J, Finney J. The declining efficacy of naltrexone pharmacotherapy for alcohol use disorders over time: a multivariate meta-analysis. Alcohol Clin Exp Res 2013 Jun;37(6):1064-8.	Meta-analysis
55	Diehl A, Ulmer L, Mutschler J, Herre H, Krumm B, Croissant B, et al. Why is disulfiram superior to acamprosate in the routine clinical setting? A retrospective long-term study in 353 alcohol-dependent patients. Alcohol Alcohol 2010 May;45(3):271-7.	Population had received detoxification treatment
56	Dolan SL, Rohsenow DJ, Martin RA, Monti PM. Urge-specific and lifestyle coping strategies of alcoholics: relationships of specific strategies to treatment outcome. Drug Alcohol Depend 2013 Feb 1;128(1-2):8-14.	Predictor study
57	Donovan DM, Anton RF, Miller WR, Longabaugh R, Hosking JD, Youngblood M. Combined pharmacotherapies and behavioral interventions for alcohol dependence (The COMBINE Study): examination of posttreatment drinking outcomes. J Stud Alcohol Drugs 2008 Jan;69(1):5-13.	Abstinent on entry

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
58	Dranitsaris G, Selby P, Negrete JC. Meta-analyses of placebo-controlled trials of acamprosate for the treatment of alcohol dependence: impact of the combined pharmacotherapies and behavior interventions study. J Addict Med 2009 Jun;3(2):74-82.	Meta-analysis
59	Drobes DJ, Anton RF, Thomas SE, Voronin K. A clinical laboratory paradigm for evaluating medication effects on alcohol consumption: naltrexone and nalmefene. Neuropsychopharmacology 2003 Apr;28(4):755-64.	Pharmacological intervention alone
60	Drobes DJ, Anton RF, Thomas SE, Voronin K. Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers. Alcohol Clin Exp Res 2004 Sep;28(9):1362-70.	Pharmacological intervention alone
61	Drobes DJ, Anton RF. Drinking in alcoholics following an alcohol challenge research protocol. J Stud Alcohol 2000 Mar;61(2):220-4.	Subjects were required to abstain for the last two days; phamacological treatment alone
62	Engel R, chlin C. Different strategies of relapse prevention: a meta-analysis of drug efficiency. 8th Congress of the Association of European Psychiatrists London, UK 7 12th July , 1996 1996.	Meta-analysis; abstract
63	Erratum: Relapse prevention by acamprosate: Results from a placebo-controlled study on alcohol dependence (Archives of General Psychiatry (1996) 53 (673-680)). Archives of General Psychiatry 1996;53(12):1097.	Erratum of a study of detoxfied patients
67	Falk D, Mattson M, Fertig J, Ryan M, Litten R. Efficacy of naltrexone in COMBINE trial using percentage of subjects with no heavy drinking days as treatment outcome measure. Alcoholism: Clinical and Experimental Research 2009;33:114A.	COMBINE study, patients detoxified on entry
65	Falk D, Wang XQ, Liu L, Fertig J, Mattson M, Ryan M, et al. Percentage of subjects with no heavy drinking days: evaluation as an efficacy endpoint for alcohol clinical trials. Alcohol Clin Exp Res 2010 Dec;34(12):2022-34.	Pooled study; COMBINE abstinent on entry
66	Farren CK, Scimeca M, Wu R, Malley SO. A double-blind, placebo-controlled study of sertraline with naltrexone for alcohol dependence. Drug Alcohol Depend 2009 Jan 1;99(1-3):317-21.	Abstinent on entry
67	Feeney GF, Young RM, Connor JP, Tucker J, McPherson A. Cognitive behavioural therapy combined with the relapse-prevention medication acamprosate: are short-term treatment outcomes for alcohol dependence improved? Aust N Z J Psychiatry 2002 Oct;36(5):622-8.	Abstinent on entry
68	Feeney GFX, Connor JP, Young RM, Tucker J, Czajkowski F. Adherence with naltrexone prescription advice in hospital outpatient alcohol rehabilitation programme. Journal of Clinical Pharmacy and Therapeutics 2001;26(1):73-9.	Abstinent on entry
69	Feeney GFX, Connor JP, Young RM, Tucker J, McPherson A. Alcohol dependence: The impact of cognitive behaviour therapy with or without naltrexone on subjective health status. Australian and New Zealand Journal of Psychiatry 2004;38(10):842-8.	Abstinent on entry
70	Feeney GFX, Young RM, Connor JP, Tucker J, McPherson A. Outpatient cognitive behavioural therapy programme for alcohol dependence: Impact of naltrexone use on outcome. Australian and New Zealand Journal of Psychiatry 2001;35(4):443-8.	Abstinent on entry

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
71	Feinn R, Kranzler HR. Does effect size in naltrexone trials for alcohol dependence differ for single-site vs. multi-center studies? (Structured abstract). Alcoholism: Clinical and Experimental Research 2005;29:983-8.	Meta-analysis
72	Feinn R, Kranzler HR. Does effect size in naltrexone trials for alcohol dependence differ for single-site vs. multi-center studies? Alcohol Clin Exp Res 2005 Jun;29(6):983-8.	Meta-analysis
73	Feinn R, Tennen H, Cramer J, Kranzler HR. Measurement and prediction of medication compliance in problem drinkers. Alcohol Clin Exp Res 2003 Aug;27(8):1286-92.	Not alcohol dependent
74	Florez G, Garcia-Portilla P, Alvarez S, Saiz PA, Nogueiras L, Bobes J. Using topiramate or naltrexone for the treatment of alcohol-dependent patients. Alcohol Clin Exp Res 2008 Jul;32(7):1251-9.	Detoxified prior to entry
75	Florez G, Saiz PA, Garcia-Portilla P, Alvarez S, Nogueiras L, Bobes J. Topiramate for the treatment of alcohol dependence: comparison with naltrexone. Eur Addict Res 2011;17(1):29-36.	Detoxified prior to randomization
76	Fl£rez G, Saiz PA, GarcÆa-Portilla P, -lvarez S, Nogueiras L, Bobes J. Amisulpride en el tratamiento de la dependencia alcoh£lica. Adicciones 2011;23(2):149-56.	Non-English language
77	Francois C, Rahhali N, Chalem Y, Torup L, Sorensen P, Luquiens A, et al. Consequences of the reduction of alcohol consumption on patient's reported outcomes with the use of nalmefene. Value in Health 2013;16(3):A63.	Pooled analysis
78	Galarza NJ, Diaz RD, Guzman F, Caballero JA, Martinez AJ. The use of naltrexone to treat ambulatory patients with alcohol dependence. Bol Asoc Med P R 1997 Oct;89(10-12):157-60.	Goal of abstinence
79	Galloway GP, Koch M, Cello R, Smith DE. Pharmacokinetics, safety, and tolerability of a depot formulation of naltrexone in alcoholics: an open-label trial. BMC Psychiatry 2005;5:18.	Abstinent on entry
80	Gammeter R. Connaissances actuelles sur l'efficacitq de la naltrexone en alcoologie. Alcoologie et Addictologie 2005;27(3):227-32.	Non-English language
81	Garbutt JC, Bonn MJ, Berger L, Longo L, Fisher M, Ford A, et al. Placebo-controlled trial of acamprosate with brief intervention for alcohol dependence in a Primary Care setting. Alcoholism: Clinical and Experimental Research 2009;33:115A.	Abstinent on entry
82	Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA 2005 Apr 6;293(13):1617-25.	Injectable naltrexone (not available in Europe)
83	Garbutt JC, West SL, Carey TS, Lohr KN, Crews FT. Pharmacological treatment of alcohol dependence: a review of the evidence. JAMA 1999 Apr 14;281(14):1318-25.	Systematic review
84	Garson JK, Gent LC, Dundon WD, Courtright LE, Pettinati HM, Oslin DW. Further evidence supporting the relationship of the therapeutic alliance and treatment outcome when utilizing medical-based interventions. Alcoholism: Clinical and Experimental Research 2010;34(6):226A.	Level of alcohol consumption not detailed; abstract only
85	Gastfriend DR, Chalk M, McCarty D. Medication and non-medication treatment of alcohol dependence: A number needed to treat (NNT) analysis. Alcoholism: Clinical and Experimental Research 2013;37:18A.	Comparison of trials, NNT-analysis

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
86	Gastfriend DR, Dong Q, Loewy J, Silverman B, Ehrich EW. Durability of Effect of Long-Acting Injectable Naltrexone. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21 26 ; Atlanta , GA 2005;NR280.	Level of alcohol consumption not detailed; abstract only
87	Gromov I, Kaempf G, Silverman B, Gastfriend DR, Cisler R. Impact on counseling and recovery activities of alcohol dependence treatment with injectable extended-release naltrexone. Substance Abuse 2009;30(2):192-3.	Level of alcohol consumption not detailed; abstract only
88	Gual A, He Y, Torup L, van den Brink W, Mann K. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. Eur Neuropsychopharmacol 2013 Apr 3.	Nalmefene
89	Gual A, He Y, Torup L, van den Brink W, Mann K. Esense 2: A randomised, double-blind, placebo-controlled study of nalmefene, as-needed use in alcohol dependent patients. Alcoholism: Clinical and Experimental Research 2012;36:246A.	Level of alcoholc consumption not detailed; abstract only
90	Gual A, He Y, Torup L, van den Brink W, Mann K. Randomised, double-blind, placebo-controlled study of nalmefene in patients with alcohol dependence. Alcoholism: Clinical and Experimental Research 2012;36:137A.	Level of alcoholc consumption not detailed; abstract only
91	Gual A, Lehert P. Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. Alcohol Alcohol 2001 Sep;36(5):413-8.	Objective to achieve abstinence
92	Guardia J, Caso C, Arias F, Gual A, Sanahuja J, Ramirez M, et al. A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder: results from a multicenter clinical trial. Alcohol Clin Exp Res 2002 Sep;26(9):1381-7.	Abstinent on entry
93	Hammarberg A, Jayaram-Lindstrom N, Beck O, Franck J, Reid MS. The effect of acamprosate on alcohol-priming induced craving. Alcoholism: Clinical and Experimental Research 2010;34:70A.	Level of alcohol consumption not detailed; abstract only
94	Hammarberg A, Jayaram-Lindstrom N, Beck O, Franck J, Reid MS. The effects of acamprosate on alcohol-cue reactivity and alcohol priming in dependent patients: a randomized controlled trial. Psychopharmacology (Berl) 2009 Jul;205(1):53-62.	Pharmacological treatment alone
95	Hammarberg A, Nylander I, Zhou Q, Jayaram-Lindstrom N, Reid MS, Franck J. The effect of acamprosate on alcohol craving and correlation with hypothalamic pituitary adrenal (HPA) axis hormones and beta-endorphin. Brain Res 2009 Dec 11;1305 Suppl:S2-S6.	Pharmacoloical treatment alone
96	Hammarberg A, Wennberg P, Beck O, Franck J. A comparison of two intensities of psychosocial intervention for alcohol dependent patients treated with acamprosate. Alcohol Alcohol 2004 May;39(3):251-5.	Abstinent prior to entry
97	Han DH, Lyool IK, Sung YH, Lee SH, Renshaw PF. The effect of acamprosate on alcohol and food craving in patients with alcohol dependence. Drug Alcohol Depend 2008 Mar 1;93(3):279-83.	Detoxified patients
98	Heinala P, Alho H, Kuoppasalmi K, Lonnqvist JK, Sinclair D, Kiianmaa K. Naltrexone in alcoholism treatment: patient efficacy and compliance. 152nd Annual Meeting of the American Psychiatric Association Washington DC , USA 15 20th May , 1999 1999.	Level of alcohol consumption not detailed; abstract only
99	Hermos JA, Young MM, Gagnon DR, Fiore LD. Patterns of dispensed disulfiram and naltrexone for alcoholism treatment in a veteran patient population. Alcohol Clin Exp Res 2004 Aug;28(8):1229-35.	Presciption usage

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No.	**Reference**	**Reason for exclusion**
100	Hoes MJAJ. Relapse prevention in alcoholics. A review of acamprosate versus naltrexone. Clinical Drug Investigation 1999;17(3):211-6.	Systematic review
101	Huang X, Huang X, Peng H, Mai G. Placebo-controlled trial of naltrexone in outpatient treatment of alcohol dependence. Chinese Mental Health Journal 2002;16:302-3.	Non-English language
102	INTEGRAL study: Acamprosate and short intervention for alcohol withdrawal. Deutsche Apotheker Zeitung 1998;138(36):28-30.	Non-English language
103	Izquierdo M, Rodriguez-Martos A, Llopis J, Ca±uelo B, Guigou G, Izquierdo J, et al. Uso de naltrexona en la deshabituaci£ n de pacientes con dependencia de alcohol en el estado espa±ol. Adicciones 2002;14(3):327-35.	Non-English language
104	Izquierdo M, Rodriguez-Martos A, Llopis J, Canuelo B, Guigou G, Izquierdo J, et al. Use of naltrexone in the rehabilitation of Spanish alcohol dependent patients. Adicciones 2002;14(3):327-35.	Non-English language
105	Jarosz J, Miernik K, Wachal M, Walczak J, Krumpl G. Naltrexone (50 mg) plus psychotherapy in alcohol-dependent patients: a meta-analysis of randomized controlled trials (Provisional abstract). Database of Abstracts of Reviews of Effects 2013;144-60.	Meta-analysis; duplicate
106	Jarosz J, Miernik K, Wachal M, Walczak J, Krumpl G. Naltrexone (50 mg) plus psychotherapy in alcohol-dependent patients: a meta-analysis of randomized controlled trials. Am J Drug Alcohol Abuse 2013 May;39(3):144-60.	Meta-analysis
107	Jarosz J, Miernik K, Wachal M, Walczak J. Clinical effectiveness analysis of naltrexone versus acamprosate and PLACEBO in alcohol dependent patients treated with psychotherapy [conference abstract]. Value in health [abstracts from the 16th annual international meeting of the international society for pharmacoeconomics and outcomes research, ISPOR 2011 baltimore, MD united states 21 25 may 2011] 2011.	Systematic review abstract
108	Jarosz J, Miernik K, Wachal M, Walczak J. Clinical effectiveness analysis of naltrexone versus acamprosate and placebo in alcohol dependent patients treated with psychotherapy. Value in Health 2011;14(3):A187-A188.	Systematic review/meta-analysis; abstract
109	Johnson BA, Ait-Daoud N, Prihoda TJ. Combining ondansetron and naltrexone effectively treats biologically predisposed alcoholics: from hypotheses to preliminary clinical evidence. Alcohol Clin Exp Res 2000 May;24(5):737-42.	Goal of abstinence
110	Kampman KM, Pettinati HM, Lynch KG, Xie H, Dackis C, Oslin DW, et al. Initiating acamprosate within-detoxification versus post-detoxification in the treatment of alcohol dependence. Addict Behav 2009 Jun;34(6-7):581-6.	Detoxification
111	Karhuvaara S, Simojoki K, Virta A, Rosberg M, Loyttyniemi E, Nurminen T, et al. Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. Alcohol Clin Exp Res 2007 Jul;31(7):1179-87.	Not alcohol-dependent
112	Kiefer F, Jahn H, Briken P, Kämpf P, Holzbach R, Naber D, et al. Naltrexone versus acamprosate in the relapse prevention of alcoholism: A randomized placebo controlled trial. European Neuropsychopharmacology 2002;12 Suppl 3:S391.	Detoxified patients

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No.	Reference	Reason for exclusion
113	Kiefer F, Jahn H, Holzbach R, Briken P, Stracke R, Wiedemann KI. Die NALCAM-Studie: Wirksamkeit, VertrSglichkeit, Outcome. Sucht: Zeitschrift fnr Wissenschaft und Praxis 2003;49(6):342-51.	Non-English language
114	Kiefer F, Jahn H, Otte C, Nakovics H, Wiedemann K. Effects of treatment with acamprosate on beta-endorphin plasma concentration in humans with high alcohol preference. Neurosci Lett 2006 Aug 14;404(1-2):103-6.	Detoxified patients
115	Kiefer F, Wiedemann K, Naber D, Jahn H, Briken P, Holzbach R. Acamprosate vs. Naltexone in relapse prevention of alcoholism: a double-blind, placebo-controlled study. XI World Congress of Psychiatry , Hamburg , August 6 11, 1999 1999;Abstracts Volume II:248.	Relapse prevention
116	Killeen TK, Brady KT, Gold PB, Simpson KN, Faldowski RA, Tyson C, et al. Effectiveness of naltrexone in a community treatment program. Alcohol Clin Exp Res 2004 Nov;28(11):1710-7.	Co-ocurring disorders/addiction allowed
117	Kiritze-Topor P, Huas D, Rosenzweig C, Comte S, Paille F, Lehert P. A pragmatic trial of acamprosate in the treatment of alcohol dependence in primary care. Alcohol Alcohol 2004 Nov;39(6):520-7.	Detoxified
118	Kleber HD, Weiss RD, Anton Jr RF, George TP, Greenfield SF, Kosten TR, et al. Treatment of patients with substance use disorders: Second edition. American Journal of Psychiatry 2006;163(8 SUPPL.):1-81.	Guidelines
119	Knox PC, Donovan DM. Using naltrexone in inpatient alcoholism treatment. J Psychoactive Drugs 1999 Oct;31(4):373-88.	Alcohol/drug dependent patients
120	Knox PC. Reducing craving and recidivism with naltrexone in inpatient alcoholism treatment, a clinical study. US: ProQuest Information & Learning; 1997.	Patients could be dependent on other drugs
121	Kopczynska E, Lampka M, Torlinski L, Ziolkowski M. The level of 8-iso-prostaglandin F2a, 4-hydroxynonenal and malondialdehyde in alcohol dependent men during combined therapy. Psychiatria Polska 2002;36(2):293-302.	Non-English language
122	Kranzler HR, Armeli S, Feinn R, Tennen H. Targeted naltrexone treatment moderates the relations between mood and drinking behavior among problem drinkers. J Consult Clin Psychol 2004 Apr;72(2):317-27.	No additional relevant outcomes (analysis of Kranzler et al., 2003 study)
123	Kranzler HR, Gage A. Acamprosate efficacy in alcohol-dependent patients: summary of results from three pivotal trials. Am J Addict 2008 Jan;17(1):70-6.	Detoxified/abstinent patients at randomisation
124	Kranzler HR, Modesto-Lowe V, Nuwayser ES. Sustained-release naltrexone for alcoholism treatment: a preliminary study. Alcohol Clin Exp Res 1998 Aug;22(5):1074-9.	Abstinent on entry
125	Kranzler HR, Modesto-Lowe V, Van KJ. Naltrexone vs. nefazodone for treatment of alcohol dependence. A placebo-controlled trial. Neuropsychopharmacology 2000 May;22(5):493-503.	Abstinent at entry
126	Kranzler HR, Tennen H, Penta C, Bohn MJ. Targeted naltrexone treatment of early problem drinkers. Addict Behav 1997 May;22(3):431-6.	Mixed population with alcohol abuse
127	Kranzler HR, Van KJ. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res 2001 Sep;25(9):1335-41.	Meta-analysis

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No.	**Reference**	**Reason for exclusion**
128	Kranzler HR, Wesson DR, Billot L. Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. Alcohol Clin Exp Res 2004 Jul;28(7):1051-9.	Detoxified on entry
129	Kruse MI, Radnovich AJ, Kalapatapu RK, Mehdiyoun N, Chambers RA, Davidson D. Effects of alcohol availability, access to alcohol, and naltrexone on self-reported craving and patterns of drinking in response to an alcohol-cue availability procedure. J Stud Alcohol Drugs 2012 Mar;73(2):205-15.	Required to be abstinent on entry
130	Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA. Naltrexone in the treatment of alcohol dependence. N Engl J Med 2001 Dec 13;345(24):1734-9.	Abstinent at entry
131	Laaksonen E, Alho H, Salaspuro M. Supervised disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence: A randomized controlled study. Proceedings of the 66th Annual Scientific Meeting of College on Problems of Drug Dependence; 2004 June 12 17; San Juan , Puerto Rico 2004.	Guidelines
132	Laaksonen E, Koski-Jannes A, Salaspuro M, Ahtinen H, Alho H. A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. Alcohol Alcohol 2008 Jan;43(1):53-61.	Open label trial without placebo control arm
133	Laaksonen E, Vuoristo-Myllys S, Koski-Jannes A, Alho H. Combining Medical Treatment and CBT in Treating Alcohol-Dependent Patients: Effects on Life Quality and General Well-Being. Alcohol Alcohol 2013 Jun 28.	Open label trial without placebo control arm
134	Landabaso MA, Iraurgi I, Sanz J, Calle R, Ruiz De Apodaka J, Jimenez-Lerma JM, et al. Naltrexone in the treatment of alcoholism. Two-year follow up results. European Journal of Psychiatry 1999;13(2):97-105.	Detoxified patients
135	Latt NC, Jurd S, Houseman J, Wutzke SE. Naltrexone in alcohol dependence: a randomised controlled trial of effectiveness in a standard clinical setting. Med J Aust 2002 Jun 3;176(11):530-4.	Detoxified before commencing trial
136	Lee JD, Grossman E, DiRocco D, Truncali A, Hanley K, Stevens D, et al. Extended-release naltrexone for treatment of alcohol dependence in primary care. J Subst Abuse Treat 2010 Jul;39(1):14-21.	Injectable naltrexone (not available in Europe)
137	Lee JD, Grossman E, Huben L, Manseau M, McNeely J, Rotrosen J, et al. Extended-release naltrexone plus medical management alcohol treatment in primary care: Findings at 15 months. Journal of Substance Abuse Treatment 2012;43(4):458-62.	Injectable naltrexone (not available in Europe)
138	Lee KS, Jeong JY, Kim DJ. Comparisons of naltrexone and acamprosate's medication compliance for 12 months in patients with alcohol dependence. Alcoholism: Clinical and Experimental Research 2012;36:33A.	Level of alcoholc consumption not detailed; abstract only
139	Lehert P, Mason B. Acamprosate for improving controlled drinking: Impact of treatment duration on therapy success. Alcohol and Alcoholism 2011;46:i31.	Meta-analysis; abstract
140	Lehert P, Potgieter AS. Markov process applied to assess alcohol abstinence. Meta-analysis on 12 acamprosate versus placebo trials. Sixth World Congress of Biological Psychiatry, Nice , France June 22 27 , 1997 1997.	Meta-analysis; abstract
141	Lehert P, VandenBrink W. Does acamprosate improve control of drinking as well as aiding abstinence? An individual patient data meta-analysis of 16 studies. Alcohol and Alcoholism 2011;46:i36.	Meta-analysis; abstract

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No.	**Reference**	**Reason for exclusion**
142	Lhuintre JP, Moore N, Tran G, Steru L, Langrenon S, Daoust M, et al. Acamprosate appears to decrease alcohol intake in weaned alcoholics. Alcohol Alcohol 1990;25(6):613-22.	Pharmacological treatment alone
143	Litten RZ, Castle IJ, Falk D, Ryan M, Fertig J, Chen CM, et al. The Placebo Effect in Clinical Trials for Alcohol Dependence: An Exploratory Analysis of 51 Naltrexone and Acamprosate Studies. Alcohol Clin Exp Res 2013 Jul 24.	Meta-analysis
144	Lobmaier PP, Kunoe N, Gossop M, Waal H. Naltrexone depot formulations for opioid and alcohol dependence: a systematic review. CNS Neurosci Ther 2011 Dec;17(6):629-36.	Systematic review
145	LoCastro JS, Youngblood M, Cisler RA, Mattson ME, Zweben A, Anton RF, et al. Alcohol treatment effects on secondary nondrinking outcomes and quality of life: the COMBINE study. J Stud Alcohol Drugs 2009 Mar;70(2):186-96.	Abstinent on entry
146	Longabaugh R, Wirtz PW, Gulliver SB, Davidson D. Extended naltrexone and broad spectrum treatment or motivational enhancement therapy. Psychopharmacology (Berl) 2009 Oct;206(3):367-76.	Abstinent on entry
147	Lucey MR, Silverman BL, Illeperuma A, O'Brien CP. Hepatic safety of once-monthly injectable extended-release naltrexone administered to actively drinking alcoholics. Alcohol Clin Exp Res 2008 Mar;32(3):498-504.	Injectable naltrexone (not available in Europe)
148	Lukas SE, Lowen SB, Lindsey KP, Conn N, Tartarini W, Rodolico J, et al. Extended-release naltrexone (XR-NTX) attenuates brain responses to alcohol cues in alcohol-dependent volunteers: a bold FMRI study. Neuroimage 2013 Sep;78:176-85.	Detoxified patients
149	Lynch K, Courtright L, Zaharakis N, Kampman K, Pettinati HM, McKay J, et al. Extending treatment effectiveness of naltrexone: A sequential randomized trial. Alcoholism: Clinical and Experimental Research 2009;33:113A.	Level of alcohol consumtion not detailed; abstract only
150	Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? (Provisional abstract). Database of Abstracts of Reviews of Effects 2013;275-93.	Meta-analysis; duplicate
151	Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? Addiction 2013 Feb;108(2):275-93.	Meta-analysis
152	Mann K, Bladstrom A, Torup L, Gual A, van den Brink W. A new treatment paradigm: Nalmefene reduces alcohol consumption in patients with alcohol dependence. Alcoholism: Clinical and Experimental Research 2012;36:138A.	Level of alcoholc consumption not detailed; abstract only
153	Mann K, Bladstrom A, Torup L, Gual A, van den Brink W. Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. Biol Psychiatry 2013 Apr 15;73(8):706-13.	Nalmefene
154	Mann K, Bladstrom A, Torup L, Gual A, van den Brink W. Shifting the paradigm: E1 - A randomised, double-blind, placebocontrolled study of nalmefene, as-needed use in alcohol dependent patients. Alcoholism: Clinical and Experimental Research 2012;36:246A.	Level of alcoholc consumption not detailed; abstract only

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No.	**Reference**	**Reason for exclusion**
155	Mann K, Bladstrom A, Torup L, Gual A, van den Brink W. Shifting the paradigm: Reduction of alcohol consumption in alcohol dependent patients - A randomised, double-blind, placebo-controlled study of nalmefene, as-needed use. European Psychiatry 2012;27.	Not clear if phamacological alone, abstract only
156	Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis (Structured abstract). Alcoholism: Clinical and Experimental Research 2004;28:51-63.	Meta-analysis; duplicate
157	Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. Alcohol Clin Exp Res 2004 Jan;28(1):51-63.	Meta-analysis
158	Mann K, Lemenager T, Hoffmann S, Reinhard I, Hermann D, Batra A, et al. Results of a double-blind, placebo-controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. Addict Biol 2012 Dec 12.	Detoxified patients
159	Mann K. A placebo controlled RCT of nalmefene to nullreduce consumptionnull in alcoholism, a paradigm shift? Alcoholism: Clinical and Experimental Research 2012;36:358A.	Level of alcoholc consumption not detailed; abstract only
160	Mann K. A potential new treatment for alcohol dependence: Results from nalmefene phase III clinical program. European Neuropsychopharmacology 2012;22:S450.	Comment on three studies
161	Marin Mayor M, Lopez Alvarez J, Riaza Perez MD, Quintana Perez A, Rubio Valladolid G. Use of anticonvulsant agents in the management of alcohol dependence. European Psychiatry 2011;26.	Systematic review; abstract
162	Martin PR, Loewy J, Liou S, Silverman B, Ehrich E. Correlation of Serum Gamma-Glutamyl Transferase With Alcohol Consumption. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21 26 ; Atlanta , GA 2005;NR215.	Pharmacotherapy alone
163	Martinotti G, Di NM, Di GM, Janiri L. Aripiprazole in the treatment of patients with alcohol dependence: a double-blind, comparison trial vs. naltrexone. J Psychopharmacol 2009 Mar;23(2):123-9.	Goal of abstinence
167	Martinotti G, Di NM, Tedeschi D, Andreoli S, Reina D, Pomponi M, et al. Pregabalin versus naltrexone in alcohol dependence: a randomised, double-blind, comparison trial. J Psychopharmacol 2010 Sep;24(9):1367-74.	Goal of abstinence
165	Mason BJ, Lehert P. Acamprosate for alcohol dependence: a sex-specific meta-analysis based on individual patient data (Structured abstract). Alcoholism: Clinical and Experimental Research 2012;36:497-508.	Meta-analysis; duplicate
166	Mason BJ, Lehert P. Acamprosate for alcohol dependence: a sex-specific meta-analysis based on individual patient data. Alcohol Clin Exp Res 2012 Mar;36(3):497-508.	Meta-analysis
167	Mason BJ, Light JM, Ciraulo D, Cisler R, Swift R, Zweben A. Effects of acamprosate in the COMBINE study: A cell x cell comparison. Alcoholism: Clinical and Experimental Research 2009;33:297A.	COMBINE patients detoxified on entry
168	Mason BJ, Salvato FR, Cutler RB, Williams LD. Nalmefene modification of alcoholism. 10th European College of Neuropsychopharmacology Congress Vienna , Austria 13th 17th September 1997 1997.	Level of alcohol consumption not reported; abstract only

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
169	Matz J, Graff C, Vainio PJ, Kallio A, Hojer AM, Struijk JJ, et al. Effect of nalmefene 20 and 80 mg on the corrected QT interval and T-wave morphology: a randomized, double-blind, parallel-group, placebo- and moxifloxacin-controlled, single-centre study. Clin Drug Investig 2011 Nov 1;31(11):799-811.	Healthy subjects
170	McCaul ME, Wand GS, Eissenberg T, Rohde CA, Cheskin LJ. Naltrexone alters subjective and psychomotor responses to alcohol in heavy drinking subjects. Neuropsychopharmacology 2000 May;22(5):480-92.	Not alcohol dependent
171	Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review (Structured abstract). International Journal of Psychiatry in Medicine 2011;42:227-66.	Systematic review; duplicate
172	Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. Int J Psychiatry Med 2011;42(3):227-66.	Systematic review
173	Monti PM, Rohsenow DJ, Hutchison KE, Swift RM, Mueller TI, Colby SM, et al. Naltrexone's effect on cue-elicited craving among alcoholics in treatment. Alcohol Clin Exp Res 1999 Aug;23(8):1386-94.	Diagnosis of alcohol abuse or dependence
174	Monti PM, Rohsenow DJ, Swift RM, Gulliver SB, Colby SM, Mueller TI, et al. Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. Alcohol Clin Exp Res 2001 Nov;25(11):1634-47.	Alcohol abuse or dependence diagnosis
175	Morgan M. UK Multicentre Study of Naltrexone as Adjunctive Therapy in the Treatment of Alcoholism - Safety Results. Xth World Congress of Psychiatry, Madrid, Spain 23rd 28th August , 1996 1996.	Detoxified patients
176	Morgan MY, Landron F, Lehert P. Improvement in quality of life after treatment for alcohol dependence with acamprosate and psychosocial support. Alcohol Clin Exp Res 2004 Jan;28(1):64-77.	Enrolled in detoxification programme
177	Morgenstern J, Kuerbis AN, Chen AC, Kahler CW, Bux DA, Jr. , Kranzler HR. A randomized clinical trial of naltrexone and behavioral therapy for problem drinking men who have sex with men. J Consult Clin Psychol 2012 Oct;80(5):863-75.	100-mg dose of naltrexone (not approved in Europe)
178	Morley KC, Teesson M, Reid SC, Sannibale C, Thomson C, Phung N, et al. Naltrexone versus acamprosate in the treatment of alcohol dependence: A multi-centre, randomized, double-blind, placebo-controlled trial. Addiction 2006 Oct;101(10):1451-62.	Patients were abstinent on entry
179	Morris PL, Hopwood M, Whelan G, Gardiner J, Drummond E. Naltrexone for alcohol dependence: a randomized controlled trial. Addiction 2001 Nov;96(11):1565-73.	Abstinent on entry
180	Namkoong K, Lee BO, Lee PG, Choi MJ, Lee E. Acamprosate in Korean alcohol-dependent patients: a multi-centre, randomized, double-blind, placebo-controlled study. Alcohol Alcohol 2003 Mar;38(2):135-41.	Detoxified patients
181	Neto D, Lambaz R, Aguiar P, Chick J. Effectiveness of sequential combined treatment in comparison with treatment as usual in preventing relapse in alcohol dependence. Alcohol Alcohol 2008 Nov;43(6):661-8.	Patients were abstinent on entry
182	Ntantouti G, Kiosterakis G, Poulis E, Houtos I, Papadopoulou V. Assessment of the final outcome of a greek alcohol addiction rehabilitation treatment programme under naltrexone using the OCDS questionnaire. Alcoholism: Clinical and Experimental Research 2010;34:104A.	Mixed population

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
183	O'Brien C, Volpicelli J. Basic and Clinical Research Leading to the Use of Naltrexone in the Treatment of Alcoholism CONFERENCE ABSTRACT. 8th European College of Neuropsychopharmacology Congress Venice , Italy 30th September 4th October, 1995 1995.	Goal of abstinence
184	O'Brien C, Volpicelli J. Narcotic Antagonists in the Treatment of Alcoholism CONFERENCE ABSTRACT. XXth Collegium Internationale Neuro psychopharmacologicum Melbourne , Australia 23rd 27th June , 1996 1996.	Comment
185	O'Brien CP. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence. Curr Psychiatry Rep 2005 Oct;7(5):327-8.	Comment article on Garbutt 2005
186	Ochoa Mangado E, Arias Horcajadas F, Torres Hernbndez MA. Evaluaci£n de la seguridad del tratamiento con naltrexona en la dependencia del alcohol. Actas Espa±olas de PsiquiatrÆa 2000;28(3):161-8.	Non-English language
187	O'Malley S. Erratum: Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence: A Randomized Controlled Trial (Journal of the American Association (April 6, 2005) 293 (1617-1625)). Journal of the American Medical Association 2005;293(23):2864.	Erratum, additional financial disclosure by a co-author
188	O'Malley S. Naltrexone for heavy drinking in young adults. Alcoholism: Clinical and Experimental Research 2012;36:334A.	Young adult frequent heavy drinkers
189	O'Malley SS, Croop RS, Wroblewski JM, Labriola DF. Naltrexone in the treatment of alcohol dependence: A combined analysis of two trials. Psychiatric Annals 1995;25(11):681-8.	Pooled analysis
190	O'Malley SS, Illeperuma A, Loewy J, Ehrich E, Silverman B. Effects of Lead-in Drinking/Treatment Goal With Long-Acting Naltrexone. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21 26 ; Atlanta , GA 2005;NR256.	Abstinent on entry
191	O'Malley SS, Jaffe AJ, Chang G, Rode S, Schottenfeld R, Meyer RE, et al. Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. Arch Gen Psychiatry 1996 Mar;53(3):217-24.	Abstinent on entry
192	O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry 1992 Nov;49(11):881-7.	Abstinent on entry
193	O'Malley SS, Jaffe AJ, Rode S, Rounsaville BJ. Experience of a "slip" among alcoholics treated with naltrexone or placebo. Am J Psychiatry 1996 Feb;153(2):281-3.	Retrospective review of patients who participated in a trial with a goal of absintence
194	O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. Psychopharmacology (Berl) 2002 Feb;160(1):19-29.	Pharmacological alone
195	O'Malley SS, Robin RW, Levenson AL, GreyWolf I, Chance LE, Hodgkinson CA, et al. Naltrexone alone and with sertraline for the treatment of alcohol dependence in Alaska natives and non-natives residing in rural settings: a randomized controlled trial. Alcohol Clin Exp Res 2008 Jul;32(7):1271-83.	Patients abstinent prior to study entry

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No.	**Reference**	**Reason for exclusion**
196	O'Malley SS, Rounsaville BJ, Farren C, Namkoong K, Wu R, Robinson J, et al. Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs specialty care: a nested sequence of 3 randomized trials. Arch Intern Med 2003 Jul 28;163(14):1695-704.	Abstinent prior to entry
197	Oncken C, Van KJ, Kranzler HR. Adverse effects of oral naltrexone: analysis of data from two clinical trials. Psychopharmacology (Berl) 2001 Apr;154(4):397-402.	Some patients had coaddiction
198	Oslin D, Liberto JG, O'Brien J, Krois S, Norbeck J. Naltrexone as an adjunctive treatment for older patients with alcohol dependence. Am J Geriatr Psychiatry 1997;5(4):324-32.	Goal of absintence
199	Oslin D, Liberto JG, O'Brien J, Krois S. Tolerability of naltrexone in treating older, alcohol-dependent patients. Am J Addict 1997;6(3):266-70.	Pharmacological alone
200	Oslin DW, Lynch KG, Pettinati HM, Kampman KM, Gariti P, Gelfand L, et al. A placebo-controlled randomized clinical trial of naltrexone in the context of different levels of psychosocial intervention. Alcohol Clin Exp Res 2008 Jul;32(7):1299-308.	Patients abstinent prior to study entry
201	Oslin DW, Swift RM, Alexander M, Forman RF. Adherence monitoring of naltrexone: Literature review of clinical trials for alcohol dependence. Substance Abuse 2009;30(2):192.	Literature review
202	Overman GP, Teter CJ, Guthrie SK. Acamprosate for the adjunctive treatment of alcohol dependence. Ann Pharmacother 2003 Jul;37(7-8):1090-9.	Systematic review
203	ovb D, Ignatovi? M, Jankovi?-Gaji? J. Acamprosbt v ambulantnej lie?be pacientov so syndr£mom zbvislosti na alkohole. ?eskb a Slovenskb Psychiatrie 2002;98(7):388-92.	Non-English language
204	Palfai T, Davidson D, Swift R. Influence of naltrexone on cue-elicited craving among hazardous drinkers: the moderational role of positive outcome expectancies. Exp Clin Psychopharmacol 1999 Aug;7(3):266-73.	Social drinkers
205	Perney P, Lehert P, Mason BJ. Sleep disturbance in alcoholism: proposal of a simple measurement, and results from a 24-week randomized controlled study of alcohol-dependent patients assessing acamprosate efficacy. Alcohol Alcohol 2012 Mar;47(2):133-9.	Goal of abstinence
206	Pettinati HM, Gastfriend DR, Dong Q, Kranzler HR, O'Malley SS. Effect of extended-release naltrexone (XR-NTX) on quality of life in alcohol-dependent patients. Alcohol Clin Exp Res 2009 Feb;33(2):350-6.	Injectable naltrexone (not available in Europe)
207	Pettinati HM, O'Brien CP, Rabinowitz AR, Wortman SP, Oslin DW, Kampman KM, et al. The status of naltrexone in the treatment of alcohol dependence: specific effects on heavy drinking. J Clin Psychopharmacol 2006 Dec;26(6):610-25.	Systematic review
208	Pettinati HM, Silverman B, Battisti JJ, Forman R, Gastfriend DR. Efficacy of extended-release naltrexone based on the severity of alcohol dependence. Alcoholism: Clinical and Experimental Research 2010;34(6):277A.	Level of alcohol consumption not detailed; abstract only
209	Pettinati HM, Silverman BL, Battisti JJ, Forman R, Schweizer E, Gastfriend DR. Efficacy of extended-release naltrexone in patients with relatively higher severity of alcohol dependence. Alcohol Clin Exp Res 2011 Oct;35(10):1804-11.	Injectable naltrexone (not available in Europe)

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No.	**Reference**	**Reason for exclusion**
210	Pettinati HM, Volpicelli JR, Pierce JD, Jr. , O'Brien CP. Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. J Addict Dis 2000;19(1):71-83.	Analysis of two pooled studies
211	Poldrugo F. Acamprosate treatment in a long-term community-based alcohol rehabilitation programme. Addiction 1997 Nov;92(11):1537-46.	Abstinent at study entry
212	Ponce G, Sbnchez-GarcÆa J, Rubio G, RodrÆguez-Jimqnez R, Jimqnez-Arriero M, Palomo T. Eficacia de la naltrexona en el tratamiento de mujeres con trastorno por dependencia del alcohol. Actas Espa±olas de PsiquiatrÆa 2005;33(1):13-8.	Non-English language
213	Ray LA, Hutchison KE, MacKillop J, Miranda R, Jr. , Audette A, Swift R, et al. Effects of naltrexone during the descending limb of the blood alcohol curve. Am J Addict 2008 Jul;17(4):257-64.	Hazardous drinkers
214	Ray LA, Krull J, Hutchison KE. The effects of naltrexone among regular drinkers: Results from the COMBINE Study. Alcoholism: Clinical and Experimental Research 2009;33:114A.	COMBINE study patients detoxified on entry
215	Ray LA, MacKillop J, Leggio L, Morgan M, Hutchison KE. Effects of naltrexone on cortisol levels in heavy drinkers. Pharmacol Biochem Behav 2009 Feb;91(4):489-94.	Hazardous drinkers
216	Ray LA, Oslin DW. Naltrexone for the treatment of alcohol dependence among African Americans: results from the COMBINE Study. Drug Alcohol Depend 2009 Dec 1;105(3):256-8.	Lead-in abstinent period prior to entry
217	Reid MS, Hammarberg A, Beck O, Franck J. The effects of acamprosate on alcohol-cue reactivity and alcohol priming in alcohol dependent patients: Evidence of a therapeutic mechanism of action. Alcoholism: Clinical and Experimental Research 2009;33:297A.	Level of alcohol consumption not detailed; abstarct only
218	Reid SC, Teesson M, Sannibale C, Matsuda M, Haber PS. The efficacy of compliance therapy in pharmacotherapy for alcohol dependence: a randomized controlled trial. J Stud Alcohol 2005 Nov;66(6):833-41.	Abstinent patients
219	Richardson K, Baillie A, Reid S, Morley K, Teesson M, Sannibale C, et al. Do acamprosate or naltrexone have an effect on daily drinking by reducing craving for alcohol? Addiction 2008 Jun;103(6):953-9.	Abstinence goal
220	Rohsenow DJ, Monti PM, Hutchison KE, Swift RM, Colby SM, Kaplan GB. Naltrexone's effects on reactivity to alcohol cues among alcoholic men. J Abnorm Psychol 2000 Nov;109(4):738-42.	Diagnosis of alcohol abuse or dependence
221	Romach MK, Sellers EM, Somer GR, Landry M, Cunningham GM, Jovey RD, et al. Naltrexone in the treatment of alcohol dependence: a Canadian trial. Can J Clin Pharmacol 2002;9(3):130-6.	Goal of abstinence
222	Roozen HG, de WR, van der Windt DA, van den Brink W, De Jong CA, Kerkhof AJ. A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence. Eur Neuropsychopharmacol 2006 Jul;16(5):311-23.	Systematic review
223	Roozen HG, Waart R, Windt DA, Brink W, Jong CA, Kerkhof AJ. A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence (Structured abstract). European Neuropsychopharmacology 2006;16:311-23.	Systematic review; duplicate
224	Rosenthal RN, Gage A, Perhach J, Goodman A. Acamprosate Is Safe and Well Tolerated for the Treatment of Alcohol Dependence. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21 26 ; Atlanta , GA 2005;NR218.	Meta-analysis; abstract

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No.	**Reference**	**Reason for exclusion**
225	Rosenthal RN, Gage A, Perhach JL, Goodman AM. Acamprosate: safety and tolerability in the treatment of alcohol dependence. J Addict Med 2008 Mar;2(1):40-50.	Database of 14 selectively chosen trials; abstinent patients
226	Rosner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database Syst Rev 2010;(9):CD004332.	Systematic review
227	Rosner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2010;(12):CD001867.	Systematic review
228	Rosner S, Leucht S, Lehert P, Soyka M. Acamprosate supports abstinence, Naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes (Structured abstract). Journal of Psychopharmacology 2008;22:11-23.	Meta-analysis; duplicate
229	Rosner S, Leucht S, Lehert P, Soyka M. Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. J Psychopharmacol 2008 Jan;22(1):11-23.	Systematic review/meta-analysis
230	Rubio G, Jimenez-Arriero MA, Ponce G, Palomo T. Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. Alcohol Alcohol 2001 Sep;36(5):419-25.	Detoxified patients
231	Rubio G, Manzanares J, Lopez-Munoz F, Alamo C, Ponce G, Jimenez-Arriero MA, et al. Naltrexone improves outcome of a controlled drinking program. J Subst Abuse Treat 2002 Dec;23(4):361-6.	Doesn't state level of drinking in population, patients had to abstain in first month
232	Rush CR, Ali JA. Naltrexone does not attenuate the acute behavioral effects of ethanol or pentobarbital in humans. Behav Pharmacol 1999 Jul;10(4):401-13.	Healthy volunteers
233	Rybakowski JK, Volpicelli JR, Ziolkowski M. Drinking relapse in male alcoholics during treatment with naltrexone, lithium or carbamazepine. 152nd Annual Meeting of the American Psychiatric Association Washington DC , USA 15 20th May , 1999 1999.	Predictor study
234	Saraf G, Viswanath B, Hatti S, Malyala A, Benegal V. A comparison of baclofen and topiramate with acamprosate as anticraving agents: A naturalistic follow-up in a tertiary care de-addiction unit. Alcoholism: Clinical and Experimental Research 2012;36:247A.	Goal of abstinence
235	Sass H, Mann K, Soyka M. Drug support for prevention of relapse in alcoholic patients with acamprosate: Results of a double blind, randomized, placebo controlled study. Sucht 1996;42(5):316-22.	Non-English language
236	Sass H, Potgieter A, Lehert PH. Acamprosate and relapse prevention: Results from a pooled analysis of 11 randomised placebo-controlled trials in 3338 alcohol-dependent patients CONFERENCE ABSTRACT. 9th European College of Neuropsychopharmacology Congress Amsterdam, The Netherlands 21st 25th September , 1996 1996.	Pooled analysis; abstract only
237	Schaumberg K, Kuerbis A, Morgenstern J, Muench F. Attributions of change and self-efficacy in a randomized controlled trial of medication and psychotherapy for problem drinking. Behav Ther 2013 Mar;44(1):88-99.	Correlation/predictor study
238	Schoechlin C, Engel RR. Meta-analysis of pharmacotherapeutic trials. In: Zernig G, Saria A, Kurz M, O'Malley SS, editors.Boca Raton, FL US: CRC Press; 2000. p. 339-51.	Meta-analyis

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
239	Sharma N, Subodh BN, Madhusudan S, Chand P, Benegal V, Murthy P. Comparison of the naltrexone and acamprosate in alcohol dependence from tertiary care centre. Indian Journal of Psychiatry 2010;52:S43.	Level of alcohol consumption not detailed; abstract only
240	Sinclair J, Batel P, Kiefer F, Chick J, Sorensen P, Gual A. As-needed use of nalmefene in the treatmentof alcohol dependence. Alcoholism: Clinical and Experimental Research 2013;37:19A.	Drug utilization
241	Sinha R, Krishnan-Sarin S, Farren C, O'Malley S. Naturalistic follow-up of drinking behavior following participation in an alcohol administration study. J Subst Abuse Treat 1999 Jul;17(1-2):159-62.	Single arm follow up
242	ska E, Lampka M, ski L, kowski M. Ste?enie 8-izo-prostaglandyny F?? oraz 4-hydroksynonenalu i dialdehydu malonowego u os£b uzale?nionych od alkoholu w trakcie kompleksowej terapii odwykowej. Psychiatria Polska 2002;36(2):293-302.	Non-English language
243	Smith EJ, Lui S, Terplan M. Pharmacologic interventions for pregnant women enrolled in alcohol treatment. Cochrane Database of Systematic Reviews 2009;(3).	Systematic review
244	Snyder JL, Bowers TG. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence: a relative benefits analysis of randomized controlled trials (Structured abstract). American Journal of Drug and Alcohol Abuse 2008;34:449-61.	Duplicate
245	Snyder JL, Bowers TG. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence: a relative benefits analysis of randomized controlled trials. Am J Drug Alcohol Abuse 2008;34(4):449-61.	Systematic review/meta-analysis
246	Sousa AD, Jagtap J. An open label trial of naltrexone versus disulfiram in elderly patients with alcohol dependence. J Pak Psych Soc 2009;6:85-9.	Detoxified patients
247	Soyka M, Sass H. Acamprosate: a new pharmacotherapeutic approach to relapse prevention in alcoholism--preliminary data. Alcohol Alcohol Suppl 1994;2:531-6.	Detoxified patients
248	Srisurapanont M, Jarusuraisin N. Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials. Int J Neuropsychopharmacol 2005 Jun;8(2):267-80.	Meta-analysis
249	Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2000;(3):CD001867.	Duplicate
250	Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2002;(2):CD001867.	Ref ID 114 is an update of this
251	Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2005;(1):CD001867.	Systematic review
252	Staner L, Boeijinga P, Danel T, Gendre I, Muzet M, Landron F, et al. Effects of acamprosate on sleep during alcohol withdrawal: A double-blind placebo-controlled polysomnographic study in alcohol-dependent subjects. Alcohol Clin Exp Res 2006 Sep;30(9):1492-9.	Patients were required to have an abstinence period
253	Streeton C, Whelan G. Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials (Structured abstract). Alcohol and Alcoholism 2001;36:544-52.	Meta-analysis
254	Streeton C, Whelan G. Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. Alcohol Alcohol 2001 Nov;36(6):544-52.	Meta-analysis

** All articles not in the English language were rescreened and excluded for reasons other than language. See Appendices 1 and 2 for details.		
No.	**Reference**	**Reason for exclusion**
255	Subbaraman M. Moderation and mediation in the combine study for treatments of alcoholism. American Journal of Epidemiology 2011;173:S299.	Detoxified patients in COMBINE
256	Subbaraman MS, Lendle S, van der Laan M, Kaskutas LA, Ahern J. Cravings as a mediator and moderator of drinking outcomes in the COMBINE study. Addiction 2013 May 14.	Newly abstinent patients
257	Subbaraman MS. Moderation and mediation in the combine (combined pharmacotherapies and behavioral interventions) study. Alcoholism: Clinical and Experimental Research 2011;35:23A.	Detoxified patients in COMBINE
258	Swainston HT, Plosker GL, Keam SJ. Extended-release intramuscular naltrexone. Drugs 2006;66(13):1741-51.	Review/comment
259	Swift R, Oslin DW, Alexander M, Forman R. Adherence monitoring in naltrexone pharmacotherapy trials: a systematic review. J Stud Alcohol Drugs 2011 Nov;72(6):1012-8.	Systematic review
260	Thomas SE, Drobes DJ, Voronin K, Anton RF. Following alcohol consumption, nontreatment-seeking alcoholics report greater stimulation but similar sedation compared with social drinkers. Journal of Studies on Alcohol 2004;65(3):330-5.	Pharmacological treatment only
261	Umhau JC, Schwandt ML, Usala J, Geyer C, Singley E, George DT, et al. Pharmacologically induced alcohol craving in treatment seeking alcoholics correlates with alcoholism severity, but is insensitive to acamprosate. Neuropsychopharmacology 2011 May;36(6):1178-86.	Patients received withdrawal treatment prior to randomisation
262	van den Brink W, Aubin HJ, Bladstrom A, Torup L, Gual A, Mann K. Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level: results from a subgroup analysis of two randomized controlled 6-month studies. Alcohol Alcohol 2013 Sep;48(5):570-8.	Nalmefene
263	van den Brink W, Aubin HJ, Bladstrom A, Torup L, Gual A, Mann K. Efficacy of nalmefene as-needed in alcohol dependent patients with high drinking risk level: Subgroup analysis of two randomised controlled studies. Alcoholism: Clinical and Experimental Research 2013;37:20A.	We have the full text of this conference abstract
264	van den Brink W, Sorensen P, Torup L, Mann K, Gual A. Long-term efficacy, tolerability, and safety of nalmefene as-needed in alcohol-dependence: A randomised, double-blind, placebo-controlled study. Alcoholism: Clinical and Experimental Research 2012;36:247A.	Level of alcoholc consumption not detailed; abstract only
265	van den Brink W, Sorensen P, Torup L, Mann K, Gual A. Long-term efficacy, tolerability, and safety of nalmefene in patients with alcohol dependence. Alcoholism: Clinical and Experimental Research 2012;36:138A.	Level of alcoholc consumption not detailed; abstract only
266	Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP. Naltrexone and alcohol dependence. Role of subject compliance. Arch Gen Psychiatry 1997 Aug;54(8):737-42.	Detoxified patients
267	Weinrieb RM, Van Horn DH, McLellan AT, Alterman AI, Calarco JS, O'Brien CP, et al. Alcoholism treatment after liver transplantation: lessons learned from a clinical trial that failed. Psychosomatics 2001 Mar;42(2):110-6.	Liver transplant patients
268	West SL, Garbutt JC, Carey TS, Lux LJ, Jackman AM, Tolleson-Rinehart S, et al. Pharmacotherapy for alcohol dependence. Evid Rep Technol Assess (Summ) 1999 Jan;(3):1-5.	Systematic review

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No.	**Reference**	**Reason for exclusion**
269	Whitworth AB, Fischer F, Lesch OM, Nimmerrichter A, Oberbauer H, Platz T, et al. Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. Lancet 1996 May 25;347(9013):1438-42.	Abstinent on entry
270	Wilbourne PL. An empirical basis for the treatment of alcohol problems. US: ProQuest Information & Learning; 2005.	Systematic review
271	Witkiewitz K, Bowen S, Donovan DM. Moderating effects of a craving intervention on the relation between negative mood and heavy drinking following treatment for alcohol dependence. J Consult Clin Psychol 2011 Feb;79(1):54-63.	Prognostic
272	Wolwer W, Frommann N, Janner M, Franke PE, Scherbaum N, Lieb B, et al. The effects of combined acamprosate and integrative behaviour therapy in the outpatient treatment of alcohol dependence: a randomized controlled trial. Drug Alcohol Depend 2011 Nov 1;118(2-3):417-22.	Detoxified patients
273	Yen MH, Ko HC, Tang FI, Lu RB, Hong JS. Study of hepatotoxicity of naltrexone in the treatment of alcoholism. Alcohol 2006;38(2):117-20.	Alcohol abuse or dependence
274	Ziólkowski M, Rybakowski J, Kosmowski W, Volpicelli JR. PSYCHOLOGICAL AND CLINICAL FACTORS PREDICTING ALCOHOL ABSTINENCE DURING 16-WEEKS TREATMENT WITH NALTREXONE. 9th Congress of the Association of European Psychiatrists Copenhagen, Denmark 20 24th September 1998 1998.	Level of alcohol consumption not detailed; abstract only
275	Ziolkowski M, Rybakowski JK. Alcohol relapse prevention: pharmacoeconomics of naltrexone versus tianeptine. 52nd Institute on Psychiatric Services; 2000 October 25 29th ; Philadelphia, PA, USA 2000.	Pharmacotherapy only
276	Ziolkowski M, Rybakowski JK. Combined pharmacotherapy and psychotherapy for preventing alcohol relapse. 52nd Institute on Psychiatric Services; 2000 October 25 29th ; Philadelphia, PA, USA 2000.	Level of alcohol consumption not detailed; abstract only

Appendix 4 Outcomes data in response to question B6

Co-primary Efficacy Analysis

Table 1. Number of HDDs (Days/Month)

		Baseline		Adjusted Change From Baseline at Month 6			Difference From Placebo + PI		
Trial	**Trial Arm**	**N**	**Mean ± SD**	**N**	**Mean ± SE**	**95% CI**	**Mean ± SE**	**95% CI**	***P* Value**
ESENSE 1	Placebo + PI	167	23.1 ± 5.4	114	−8.0 ± 1.0	[−9.8, −6.1]	−3.7 ± 1.0	[−5.9; −1.5]	0.0010
	Nalmefene + PI	171	23.0 ± 5.9	85	−11.6 ± 1.0	[−13.6; −9.6]			
ESENSE 2	Placebo + PI	155	21.6 ± 6.4	111	−10.2 ± 0.9	[−12.1; −8.4]	−2.7 ± 1.2	[−5.0; −0.3]	0.0253
	Nalmefene + PI	148	22.7 ± 6.0	103	−12.9 ± 0.9	[−14.7; −11.0]			
SENSE	Placebo + PI	42	18.6 ± 6.4	29[a]	−8.6 ± 1.4[a]	[−11.3; −5.9][a]	−3.6 ± 1.5[a]	[−6.5; −0.7][a]	0.0164[a]
	Nalmefene + PI	141	19.1 ± 6.3	78[a]	−12.2 ± 0.9[a]	[−14.0; −10.4][a]			

CI = confidence interval; HDD = heavy drinking day; PI = psychosocial intervention; SD = standard deviation; SE = standard error.

[a] Month 13.

Table 2. TAC (g/day)

		Baseline		Adjusted Change From Baseline at Month 6			Difference From Placebo + PI		
Trial	**Trial Arm**	**N**	**Mean ± SD**	**N**	**Mean ± SE**	**95% CI**	**Mean ± SE**	**95% CI**	***P* Value**
ESENSE 1	Placebo + PI	167	98.7 ± 40.5	114	−40.0 ± 3.9	[−47.6; −32.3]	−18.3 ± 4.4	[−26.9; −9.7]	< 0.0001
	Nalmefene + PI	171	102.2 ± 42.9	85	−58.3 ± 4.1	[−66.4; −50.2]			
ESENSE 2	Placebo + PI	155	108.0 ± 47.4	111	−60.1 ± 4.0	[−68.0; −52.3]	−10.3 ± 5.0	[−20.2; −0.5]	0.0404
	Nalmefene + PI	148	113.0 ± 48.0	103	−70.4 ± 4.0	[−78.3; −62.6]			
SENSE	Placebo + PI	42	100.6 ± 46.9	29[a]	−49.7 ± 6.4[a]	[−62.4; −37.1][a]	−17.3 ± 6.8[a]	[−30.9; −3.8][a]	0.0129[a]
	Nalmefene + PI	141	100.4 ± 45.0	78[a]	−67.1 ± 4.3[a]	[−75.5; −58.6][a]			

CI = confidence interval; PI = psychosocial intervention; SD = standard deviation; SE = standard error; TAC = total alcohol consumed.

[a] Month 13.

Key Secondary Analysis

Table 3. RSDRL - Proportion (%) of Responders and Odds Ration for Response at Month 6

Trial	Trial Arm	N	% of Responders	OR	95% CI	*P* Value
ESENSE 1	Placebo + PI	167	42.5	2.15	[1.38; 3.36]	< 0.001
	Nalmefene + PI	171	60.8			
ESENSE 2	Placebo + PI	155	41.3	1.59	[0.98; 2.59]	0.062
	Nalmefene + PI	148	52.0			

CI = confidence interval; PI = psychosocial intervention; OR = odds ratio; RSDRL = response defined as a downward shift from baseline in DRL; for patients with a very high DRL at baseline, a shift to medium DRL or lower; for patients with a high or medium DRL at baseline, a shift to low DRL.

Other Responder Analysis

Table 4. RLDRL - Proportion (%) of Responders and Odds Ration for Response at Month 6

Trial	Trial Arm	N	% of Responders	OR	95% CI	*P* Value
ESENSE 1	Placebo + PI	167	29.3	2.12	[1.34; 3.39]	0.001
	Nalmefene + PI	171	45.6			
ESENSE 2	Placebo + PI	155	34.2	1.44	[0.86; 2.42]	0.170
	Nalmefene + PI	148	40.5			

CI = confidence interval; PI = psychosocial intervention; OR = odds ratio; RSDRL = response defined as a downward shift from baseline in DRL to low DRL or lower.

Table 5. Proportion (%) of Responders, Based on a ≥ 70% Reduction in TAC at Month 6

Endpoint	Trial Arm	N	% of Responders	OR	95% CI	*P* Value
ESENSE 1	Placebo + PI	167	21.0	2.22	[1.34; 3.72]	0.002
	Nalmefene + PI	171	35.7			
ESENSE 2	Placebo + PI	155	31.0	1.63	[0.98; 2.71]	0.058
	Nalmefene + PI	148	41.2			

CI = confidence interval; PI = psychosocial intervention; OR = odds ratio; TAC = total alcohol consumed.

Table 6. NDDs at Month 6

		Mean at Baseline		Change From Baseline at Month 6		Difference From Placebo + PI		
Trial	Trial Arm	N	Mean ± SD	N	Mean ± SE	Mean ± SE	95% CI	*P* Value
ESENSE 1	Placebo + PI	167	3.1 ± 4.3	114	4.4 ± 0.8	2.4 ± 1.0	[0.5; 4.3]	0.014
	Nalmefene + PI	171	3.3 ± 5.1	85	6.8 ± 0.9			
ESENSE 2	Placebo + PI	155	4.2 ± 5.5	111	6.6 ± 0.8	1.5 ± 1.1	[−0.6; 3.7]	0.163
	Nalmefene + PI	148	3.6 ± 5.1	103	8.2 ± 0.8			

CI = confidence interval; NDD = non-drinking day; PI = psychosocial intervention; SD = standard deviation.

Clinical Global Impression

Table 7. CGI-S

		Baseline		Adjusted Change From Baseline at Month 6			Difference From Placebo + PI		
Trial	**Trial Arm**	**N**	**Mean ± SD**	**N**	**Mean**	**95% CI**	**Mean**	**95% CI**	***P* Value**
ESENSE 1	Placebo + PI	167	4.2 ± 1.4	111	−0.7	[−0.9; −0.4]	−0.4	[−0.7; −0.1]	0.0051
	Nalmefene + PI	171	4.1 ± 1.4	83	−1.1	[−1.3; −0.8]			
ESENSE 2	Placebo + PI	154	4.3 ± 1.3	110	−0.9	[−1.1; −0.6]	−0.5	[−0.8; −0.1]	0.0050
	Nalmefene + PI	148	4.4 ± 1.3	99	−1.3	[−1.6; −1.1]			
SENSE	Placebo + PI	40	4.0 ± 1.2	30	−0.7	[−1.1; −0.4]	−0.2	[−0.6; 0.2]	0.3172
	Nalmefene + PI	135	4.0 ± 1.1	94	−0.9	[−1.1; −0.7]			

CGI-S = Clinical Global Impression – Severity of Illness; CI = confidence interval; PI = psychosocial intervention; SD = standard deviation.

Table 8. CGI-I

		Adjusted Change From Baseline at Month 6			Difference From Placebo + PI		
Trial	**Trial Arm**	**N**	**Mean**	**95% CI**	**Mean**	**95% CI**	***P* Value**
ESENSE 1	Placebo + PI	111	3.0	[2.8; 3.2]	−0.6	[−0.8; −0.3]	< 0.0001
	Nalmefene + PI	83	2.4	[2.2; 2.7]			
ESENSE 2	Placebo + PI	110	2.9	[2.6; 3.1]	−0.3	[−0.6; −0.0]	0.0425
	Nalmefene + PI	99	2.5	[2.3; 2.8]			
SENSE	Placebo + PI	30	2.9	[2.5; 3.3]	−0.3	[−0.8; 0.1]	0.1041
	Nalmefene + PI	94	2.5	[2.3; 2.8]			

CGI-I = Clinical Global Impression – Global Improvement; CI = confidence interval; PI = psychosocial intervention.

Liver Parameters

Table 9. GGT at Month 6

		Geometric Mean at Baseline		Adjusted Change From Baseline at Month 6			Ratio to Placebo + PI		
Trial	**Trial Arm**	**N**	**Mean**	**N**	**Mean**	**95% CI**	**Ratio**	**95% CI**	***P* Value**
ESENSE 1	Placebo + PI	167	60.13	112	53.90	[47.30; 61.41]	0.73	[0.64; 0.84]	< 0.0001
	Nalmefene + PI	171	55.69	87	39.46	[34.40; 45.27]			
ESENSE 2	Placebo + PI	153	54.89	108	52.42	[45.64; 60.21]	0.90	[0.76; 1.07]	0.2443
	Nalmefene + PI	148	55.90	100	47.32	[41.31; 54.20]			

CI = confidence interval; GGT = gamma-glutamyltransferase; PI = psychosocial intervention.

Table 10. ALAT at Month 6

		Geometric Mean at Baseline		Adjusted Change From Baseline at Month 6			Ratio to Placebo + PI		
Trial	**Trial Arm**	**N**	**Mean**	**N**	**Mean**	**95% CI**	**Ratio**	**95% CI**	***P* Value**
ESENSE 1	Placebo + PI	166	29.33	110	29.60	[26.84; 32.64]	0.83	[0.75; 0.93]	0.0011
	Nalmefene + PI	171	29.36	87	24.71	[22.27; 27.41]			
ESENSE 2	Placebo + PI	153	28.97	108	31.51	[28.40; 34.96]	0.85	[0.75; 0.96]	0.0100
	Nalmefene + PI	148	29.32	100	26.84	[24.29; 29.66]			

ALAT = alanine aminotransferase; CI = confidence interval; PI = psychosocial intervention.

Health-Related Quality of Life

Table 11. SF-36 at Month 6

		Baseline		Change From Baseline to Month 6		Difference From Placebo + PI		
Trial	**Trial Arm**	**N**	**Mean ± SD**	**N**	**Mean ± SE**	**Mean ± SE**	**95% CI**	***P* Value**
ESENSE 1	Physical Component Summary							
	Placebo + PI	166	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	167	[redacted]	[redacted]	[redacted]			
	Mental Component Summary							
	Placebo + PI	166	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	167	[redacted]	[redacted]	[redacted]			
ESENSE 2	Physical Component Summary							
	Placebo + PI	148	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	146	[redacted]	[redacted]	[redacted]			
	Mental Component Summary							
	Placebo + PI	148	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	146	[redacted]	[redacted]	[redacted]			

CI = confidence interval; PI = psychosocial intervention; SD = standard deviation; SE = standard error; SF-36 = SF-36 Health Survey.

Table 12. EQ-5D at Month 6

		Baseline		Change From Baseline to Month 6		Difference From Placebo + PI		
Trial	**Trial Arm**	**N**	**Mean ± SD**	**N**	**Mean ± SE**	**Mean ± SE**	**95% CI**	***P* Value**
ESENSE 1	Health State							
	Placebo + PI	164	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	170	[redacted]	[redacted]	[redacted]			
	Utility Index							
	Placebo + PI	166	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	170	[redacted]	[redacted]	[redacted]			
ESENSE 2	Health State							
	Placebo + PI	151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	147	[redacted]	[redacted]	[redacted]			
	Utility Index							
	Placebo + PI	152	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	147	[redacted]	[redacted]	[redacted]			

CI = confidence interval; EQ-5D = EuroQol 5-dimension PI = psychosocial intervention; SD = standard deviation; SE = standard error.

Table 13. DrInc-2R at Month 6

		Baseline		Change From Baseline to Month 6		Difference From Placebo + PI		
Trial	**Trial Arm**	**N**	**Mean**	**N**	**Mean ± SE**	**Mean ± SE**	**95% CI**	***P* Value**
ESENSE 1	Placebo + PI	166	35.0	133	−11.8 ± 1.5	−3.7 ± 1.6	[−6.8; −0.5]	0.022
	Nalmefene + PI	170	35.2	87	−15.5 ± 1.6			
ESENSE 2	Placebo + PI	154	48.8	105	−17.2 ± 1.1	−2.7 ± 2.5	[−7.6; 2.2]	0.284
	Nalmefene + PI	147	48.2	101	−19.9 ± 2.1			

CI = confidence interval; DrInc-2R = The Drinker Inventory of Consequences–Recent Drinking; PI = psychosocial intervention; SE = standard error.

Appendix 5: Lundbeck survey of use of psychosocial interventions in clinical practice

Respondents A-J

Practice or clinic name (primary care or specialist alcohol or addiction clinic/service)	**A** **Primary care**	**B** **Specialist**	**C** **Specialist**	**D** **Specialist**	**E** **Specialist**	**F** **Primary**	**G** **Primary**	**H** **Primary**	**I** **Primary**	**J** **Specialist**
Location	**Hertfordshire**	**Basildon, Pitsea, Essex**	**Common Lane, Hatfield.**	**North London**	**Hillingdon (CNWL)**	**Beswick**	**Beswick**	**Walsall**	**Walsall**	**Solihull**
Q1. Please describe the types of patients you currently treat for alcohol dependence e.g. in terms of units or grammmes of alcohol consumption; dependence severity; drinking risk levels; hazardous or harmful.	Patients are between 100-150 units per week.	Services are available for people aged 18 years and older in the Local Authority areas in South Essex covered by Thurrock Council, Southend Borough Council and Essex County Council. The services are primarily for people with Opiate (heroin)/Crack addictions and people physically dependent on Alcohol.	All adult patients who self refer or who are refered by primary care in Herts area.	We treat higher risk (16-19 on AUDIT) and high risk/possibly dependent patients using a range of medication for physical withdrawals, combined with structured psychosocial interventions (group and 1:1) for the psychological issues of dependence. Our patients drink varying amounts - usually 15-20 units + if physically dependent and daily at lower levels if psychologically dependent (satisfying diagnostic	We generally see patients with moderate to severe dependence. Average consumption varies but may be 140 - 300 Units of alcohol / week. We sometimes see patients with mild dependence or harmful use who are complex because of co-morbid physical and / or mental conditions.	All levels of dependence from mild to severe. Treats the mild end of alcohol dependence himself but refers to CAT team in most patients.	Sees all levels of alcohol dependence on presentation but only treats milder patients who don't need referring to CAT team. Not sure in terms of units per day.	Patients who score over 16 on FULL AUDIT (after doing FAST/AUDIT C as part of current LES).	Patients who score over 16 on FULL Audit, or patients who opportunistically present with harmful levels of drinking.	Adult patients who self refer or who are refered by primary care.

				criteria).						

Q2. For a patient who is diagnosed with alcohol dependence but who does not have physical withdrawal symptoms or need immediate detoxification, please describe your current treatment options and rationale for each option**	Brief intervention & group therapy. Consider vitamin supplement. Also CRi refferal option if required.	Consultant & Nurse led service, psychosocial intervention + below support.	Psychosocial Intervention provided by CRi Spectrum.	Offering structured Extended Brief Interventions (EBI) sessions for up to 12 weeks, with 1-6 sessions, usually in GP clinic location. Offering structured group programme with 5-6 days of activity, combined with motivational interviewing-focuse 1:1 sessions for 6-12 weeks (with option of extension if required/desired). Specialist mental health counseling for co-morbid or inter-related psychological issues - this could follow or run-alongside the group programme. Prescription arrangement for acamprosate or disulfiram in agreement with GP.	We very rarely advocate immediate detoxification and in all cases of dependence (except mild cases), we will offer 6 sessions of motivational interviewing to prepare for detox, which will then follow. Relapse management sessions will follow the detox. In mildest cases, we will still offer all the above but with no detox (relapse management follows once abstinence achieved).	Hazardous drinkers - perform brief advice, harmful onwards - refer to CAT.	Would offer brief advice and then refer to CAT team.	I offer them brief advice and ask them to abstain for 4 weeks and do blood screen. After 4 weeks if they are still drinking at hazardous levels I refer them to third sector alcohol services for a course of CBT.	I offer them brief advice and suggest they may want to reduce the amount they are drinking, no follow up arranged unless patient comes back themselves.	Psychosocial Intervention provided by Aquarius.

Q3. Which of the following types of psychosocial or psychological intervention do you use in your practice for the patients who do not require immediate detoxification? And approximately how many of these patients are offered each option?	Breakdown below-	• 1:1 support and care co-ordination	All the services listed are provided by the service, difficult to give a precise breakdown of % of patients going through the Cri sytsem as they have 8 hubs in Hertfordshire.	All estimates as difficult to get objective data on. Not sure on some of the titles	100% of patients get Motivational Enhancement (Interviewing). 5% get Cognitive behaviour therapy (but this addresses mental health conditions rather than alcohol use). We dont offer social behav network treatments. Brief interventions are not offered routinely , except on initial assessment as a precursor to motivational treatments. We dont offer these alone, so I would say 0%	Offers brief advice to all alcohol patients. CBT if feasible but often too long waiting list.	Refers to CAT team	Nothing available in practice other than brief advice and support and monitoring if the patient is able to reduce or abstain from drinking harmfully. All Psychosocial intervention provided by Addaction locally, if patients then go on to choose to self refer, or if I feel I can no longer do anything for them	Nothing available in practice other than brief advice and support, all Psychosocial intervention provided by addaction locally, if patients then go on to choose to self refer, or if I feel I can no longer do anything for them	All the services listed are provided by the service, but unable to give a breakdown of % of patients going through these
Cognitive Behavioural Based Therapies		• advice and information			5%					
Standard Cognitive Behaviour Therapy (CBT)	30%	• stabilisation		60%		20%				
Coping Skills	20%	• counselling and relapse prevention		80%						
Social Skills Training		• motivational interviewing		10%						
Relapse Prevention		• community detoxification		80%						
Behavioural Therapies		• support for service users, relatives and carers								

Cue Exposure		• substitute prescribing for opiate addiction		30%						
Behavioural Self-Control Training		• assessments for residential detoxification and rehabilitation		30%						
Contingency Management		• pre-sentence reports and liaison with criminal justice services for those who have drug or alcohol related offences		0%						
Aversion Therapy		• liaison with GPs, hospitals and rehabilitation units		5%						
Social Network and Environment Based Therapies		• facilitation of rehabilitation								
Social Behaviour and Network Therapy				20%						
The Community Reinforcement Approach				0%						
Counselling										
Couples Therapy (including behavioural couples therapy and other variants of couples therapy)				5%						
Brief Interventions (Planned only)						100%	100%			
Psychoeducational and motivational techniques				100%						
Extended brief intervention	70%			75%						

Motivational Enhancement Therapy				100%	100%					
Brief behavioural compliance enhancement (BBCET)				0%						
Other (please describe)										

Respondents K-R

Practice or clinic name (primary care or specialist alcohol or addiction clinic/service)	**K Primary**	**L Primary**	**M Specialist**	**N Specialist**	**O Primary**	**P Specialist**	**Q Primary**	**R Specialist**
Location	**Willenhall**	**Willenhall**	**South Notts**	**Stoke on Trent**	**Stoke on Trent**	**Bristol 3 locations**	**Salisbury**	**Chippenham**
Q1. Please describe the types of patients you currently treat for alcohol dependence e.g. in terms of units or grammmes of alcohol consumption; dependence severity; drinking risk levels; hazardous or harmful.	Adult patient who presented and asked for help with their drinking or someone who was moderate/severe in their dependency and needs a detox.	New patients would be questioned regarding their alcohol,if identified as high risk.	High risk drinkers, moderately to severe dependence. 15-45 units of alcohol per day.	Moderate to severe dependence over 20 units of alcohol per day. High or very high drinking risk level	15+ units per day. High risk drinkers, moderate to severe dependence.	AUDIT 8-15 BI, 16-19 (EBI).	Hazardous drinking AUDIT 8-15.	Patients referred by GP, typically AUDIT 15 and above requiring EI and detox.
Q2. For a patient who is diagnosed with alcohol dependence but who does not have physical withdrawal symptoms or need immediate detoxification, please describe your current treatment options and rationale for each option**	Would provide brief advice and tell them to reduce their drinking, no follow up arranged with them.	Nurse would provide brief intervention, would get follow up if the patient came back voluntarily, and if they could reduce their drinking on their own then would look to support further with brief advice.	Vitamin supplementation, monitoring of physical health. Extended Brief Advice.	Check Physical health, brief advice and ongoing psychosocial support.	Brief advice, ongoing psychosocial support.	Referred by GP following AUDIT. Offered Brief advice/interventio ns.	Brief advice given/Brief Interventions.Will refer to Turning Point if drinking continues at hazardous level.	SADQ 15 or less consider moderate drinking. Psychological Interventions and some naltrexone.

Q3. Which of the following types of psychosocial or psychological intervention do you use in your practice for the patients who do not require immediate detoxification? And approximately how many of these patients are offered each option?	Nothing available in practice other than brief advice and support, all Psychosocial intervention provided by Addaction locally, if patients then go on to choose to self refer, or maybe if I feel I can no longer do anything for them	Nothing available in practice other than brief advice and support, all Psychosocial intervention provided by Addaction locally, if patients then go on to choose to self refer, or maybe if I feel I can no longer do anything for them						Many different forms of therapy dependant on patient.
Cognitive Behavioural Based Therapies								
Standard Cognitive Behaviour Therapy (CBT)								20
Coping Skills							10	10
Social Skills Training								10
Relapse Prevention								10
Behavioural Therapies								
Cue Exposure								
Behavioural Self-Control Training								10%
Contingency Management								
Aversion Therapy								
Social Network and Environment Based Therapies								
Social Behaviour and Network Therapy								10%
The Community Reinforcement Approach								
Counselling								
Couples Therapy (including behavioural couples therapy and other variants of couples therapy)								10%
Brief Interventions (Planned only)			100%			50%	80%	

Psychoeducational and motivational techniques				10%	25%		10%	10%
Extended brief intervention			100%	90%	75%	50%		
Motivational Enhancement Therapy								10%
Brief behavioural compliance enhancement (BBCET)								
Other (please describe)								

Appendix 6. Quality Assessments – Pharmacological Interventions Review

Quality Assessment: Heinälä et al., 2001

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	No details on method. '121... were randomly assigned for the study after a 1-week run-in trial with a riboflavin-marked placebo.'	Not clear
Was the concealment of treatment allocation adequate?	No details on masking	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	'There were no significant differences among the four groups on any variable.'	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was a double-blind study. However, no details on method were provided.	Not clear
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Information on dropouts provided for all subjects—no information provided by treatment group.	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not clear	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes: '…results are from analyses of all patients (i.e., intent-to-treat patients) and not just those completing the study or those with high compliance.'	Yes

Quality Assessment: Kranzler et al., 2003

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	No details on method	Not clear
Was the concealment of treatment allocation adequate?	No details on masking	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no group differences on any of the baseline characteristics in terms of prognostic factors.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No details on method	Not clear
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	The proportion of patients failing to complete (due to adverse events or withdrawal of consent) was comparable among groups.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not all outcomes noted in the method were reported such as medication questionnaire results.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Hierarchical linear modeling (HLM) and analysis of covariance (ANCOVA) were used to examine the main and interactive effects of medication group (naltrexone vs. placebo) and schedule of administration (daily vs. targeted) on drinking outcomes. The HLM software accounts for missing data and differentially weights on the basis of the number of daily assessments.	No

Quality Assessment: Kranzler et al., 2009

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	No details on method	Not clear
Was the concealment of treatment allocation adequate?	No details on masking	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no group differences on any of the baseline characteristics in terms of prognostic factors.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No details on method	Not clear
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No details provided on dropouts by treatment group.	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes noted in the methods were reported in the article	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The analysis included all randomised patients. A two-level hierarchical linear model (HLM) was used to examine the main and interaction effects of medication group (naltrexone vs. placebo), schedule of administration (daily vs. targeted), and time (week in treatment) on the number of standard drinks consumed during the 12-week treatment period.	No

Appendix 7. Quality Assessments – Psychosocial Interventions Review

Quality Assessment: Brown et al., 2007

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Random assignment was stratified by participating clinic and blocked in sets of 5 experimental subjects and 5 control subjects to ensure balanced assignment of subjects within each clinic.	Yes
Was the concealment of treatment allocation adequate?	Control subjects were notified of their group assignment by mail.	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	At baseline, there were no significant differences between the experimental and control groups on demographic variables, alcohol use disorders, or alcohol consumption.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Trained assistants who collected outcomes data were blinded to subjects random assignments, and used scripts to guide telephone interviews.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No information on dropouts by treatment group	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The baseline questionnaire included various measures of readiness to change drinking, severity of alcohol dependence, psychological function, well-being, social support, and health care utilization; these data were not considered for this report.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Initially, the authors performed intention-to-treat analyses, assuming that all missing 3-month drinking data were identical to baseline, then, the authors performed responder analyses, considering only subjects who provided 3-month drinking data.	Yes

Quality Assessment: Field et al., 2010

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Patients were randomized to either treatment as usual with assessment (TAU+) or an assessment with Brief Motivational Intervention (BMI) using a permuted block design (block size 6) to ensure approximately equal distribution of patients according to their race/ethnicity.	Yes
Was the concealment of treatment allocation adequate?	Study clinicians were blinded to patient randomization prior to completion of the baseline assessment. Research staff blind to treatment assignment conducted follow up assessments by telephone at six and 12 months.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no clinically relevant differences in baseline characteristics between the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	To reduce interviewer bias, study clinicians were blinded to patient randomization prior to completion of the baseline assessment. Research staff blind to treatment assignment conducted follow up assessments by telephone at six and 12 months.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There appeared to be no differences in dropout between groups.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes were assessed as mentioned in the methodology.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No intention-to-treat analysis was reported.	No

Quality Assessment: Weinreb et al., 2011

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Type of randomisation has not been detailed.	Not clear
Was the concealment of treatment allocation adequate?	Details of concealment not provided.	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no clinically relevant differences in baseline characteristics between the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No mention of blinding of care provider, assessors or participants.	Not Clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Of the subjects who did not die, 18 of 37 (49%) dropped out of the study in the MET group and 24 of 38 (63%) dropped out of the TAU group. Although the TAU proportion is higher, the difference was not statistically significant (chi-square [1 df] = 1.07, P = 0.30).	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes were assessed as mentioned in the methodology.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No mention of intention-to treat analysis being undertaken.	No

Quality Assessment: Sobell et al., 2009

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	The 287 eligible participants were blocked on gender and primary substance problem then randomly assigned to either group treatment (GT; *n* =143) or individual treatment (IT; *n* = 144). Blocked randomization resulted in 231 alcohol abusers and 56 drug abusers assigned as follows: alcohol group treatment (AGT; *n* = 112); alcohol individual treatment (AIT; *n*== 119); drug group treatment (DGT; *n* =31); and drug individual treatment (DIT; *n* = 25).	Yes
Was the concealment of treatment allocation adequate?	Research assistants conducted the follow-up interviews and were blind to participants' treatment conditions until the last few questions at the 12-month follow-up that asked clients to evaluate their assigned treatment modality. Collaterals were also interviewed by phone at 6- and 12-months by a research assistant blind to the participants' treatment assignment.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Statistical comparisons found no significant differences (P > 0.001) between the individual treatment and group treatment conditions	No
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Research assistants conducted the follow-up interviews and were blind to participants' treatment conditions until the last few questions at the 12-month follow-up that asked clients to evaluate their assigned treatment modality. Collaterals were also interviewed by phone at 6- and 12-months by a research assistant blind to the participants' treatment assignment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	For the 264 participants who entered treatment, there were no statistically significant (*p* > .05) differences in retention rates between the individual treatment and group therapy conditions	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes were assessed as mentioned in the methodology.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Examination of treatment effectiveness was conducted as intent to treat analyses using a piece-wise linear random effects model for analyzing longitudinal data. This procedure assumes that data are available for a random sample of participants after the completion of treatment. For missing data, parameter estimation was performed using maximum likelihood estimation.	Yes

Quality Assessment: Walitzer et al., 2009

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Random assignment to condition was conducted by the third author via urn randomization to balance life-time Alcoholics Anonymous involvement scores across conditions.	Yes
Was the concealment of treatment allocation adequate?	Research interviewers were blind to intervention condition	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no significant differences among experimental conditions.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Research interviewers were blind to intervention condition.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Dropout rate was non-significant across groups.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes were assessed as mentioned in the methodology.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Of 297 eligible callers, 224 presented for an intake interview, ultimately yielding an intent-to-treat sample of 169 individuals (57 women). Methods of accounting for missing data not reported.	Yes

Quality Assessment: Wiers et al., 2011

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Details of randomisation type not included. Patients were assigned randomly to one of four conditions.	Not clear
Was the concealment of treatment allocation adequate?	Therapists were blind to whether the training was real or sham, but they knew which group was the no-training control group.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no clinically relevant differences in baselines characteristics between the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Therapists were blind to whether the training was real or sham, but they knew which group was the no-training control group.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no significant differences between experimental and control groups with respect to baseline characteristics	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes were assessed as mentioned in the methodology.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Methods of accounting for missing data not reported.	Yes

Quality Assessment: Jung et al., 2011

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Subjects were allocated into one of two groups through one-to-one randomization by admission order	Yes
Was the concealment of treatment allocation adequate?	No information on masking.	Not clear.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no clinically relevant differences in baseline characteristics between the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No mention of blinding within the study.	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There was no patient who did not complete the intervention.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes notes in the methods were reported in the manuscript	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	An intention-to-treat analysis was not included in this study.	No

Appendix 8 Safety outcomes responses to question B19

Safety

Table 14. TEAEs With an Incidence of 5% or More, by Preferred Term (APTS): ESENSE 1: Total Population

	Nalmefene + PI		Placebo + PI	
	n = 302		n = 296	
TEAE	**N**	**%**	**n**	**%**
Patients with TEAEs	246	81.5	198	66.9
Dizziness	83	27.5	23	7.8
Nausea	83	27.5	18	6.1
Fatigue	53	17.5	25	8.4
Headache	36	11.9	27	9.1
Nasopharyngitis	34	11.3	37	12.5
Sleep disorder	32	10.6	1	0.3
Insomnia	30	9.9	10	3.4
Vomiting	24	7.9	8	2.7
Hyperhidrosis	16	5.3	5	1.7

APTS = all patients treated set; PI = psychosocial intervention; TEAE = treatment-emergent adverse event.

Table 15. TEAEs With an Incidence of 5% or More, by Preferred Term (APTS): ESENSE1: Licensed Population

	Nalmefene + PI		Placebo + PI	
	n = 179		n = 169	
TEAE	**N**	**%**	**n**	**%**
Patients with TEAEs	149	83.2	124	73.4
Dizziness	56	31.3	12	7.1
Nausea	51	28.5	12	7.1
Fatigue	30	16.8	16	9.5
Sleep disorder	28	15.6	1	0.6
Headache	27	15.1	18	10.7
Insomnia	20	11.2	3	1.8
Nasopharyngitis	18	10.1	27	16.0
Vomiting	15	8.4	5	3.0
Decreased appetite	11	6.1	3	1.8
Hyperhidrosis	11	6.1	3	1.8
Back pain	10	5.6	9	5.3
Dry mouth	9	5.0	3	1.8
Hypoaesthesia	9	5.0	1	0.6
Diarrhoea	8	4.5	12	7.1
Accidental overdose	4	2.2	11	6.5

APTS = all patients treated set; PI = psychosocial intervention; TEAE = treatment-emergent adverse event.

Table 16. TEAEs With an Incidence of 5% or More, by Preferred Term (APTS): ESENSE 2: Total Population

	Nalmefene + PI		Placebo + PI	
	n = 341		n = 337	
TEAE	**N**	**%**	**n**	**%**
Patients with TEAEs	232	68.0	199	59.1
Nausea	58	17.0	20	5.9
Dizziness	52	15.2	15	4.5
Insomnia	49	14.4	22	6.5
Headache	43	12.6	26	7.7
Nasopharyngitis	19	5.6	17	5.0
Vomiting	19	5.6	8	2.4
Diarrhoea	8	2.3	17	5.0

APTS = all patients treated set; PI = psychosocial intervention; TEAE = treatment-emergent adverse event.

Table 17. TEAEs With an Incidence of 5% or More, by Preferred Term (APTS): ESENSE 2: Licensed Population

	Nalmefene + PI		Placebo + PI	
	n = 152		n = 158	
TEAE	**N**	**%**	**n**	**%**
Patients with TEAEs	107	70.4	96	60.8
Insomnia	29	19.1	12	7.6
Nausea	27	17.8	11	7.0
Dizziness	22	14.5	9	5.7
Headache	19	12.5	15	9.5
Vomiting	10	6.6	7	4.4
Decreased appetite	8	5.3	1	0.6

	Nalmefene + PI		Placebo + PI	
	n = 152		n = 158	
TEAE	**N**	**%**	**n**	**%**
Nasopharyngitis	8	5.3	9	5.7
Tremor	8	5.3	7	4.4
Diarrhoea	4	2.6	9	5.7

APTS = all patients treated set; PI = psychosocial intervention; TEAE = treatment-emergent adverse event.

Table 18. TEAEs With an Incidence of 5% or More, by Preferred Term (APTS): SENSE: Total Population

	Nalmefene + PI		Placebo + PI	
	n = 501		n = 164	
TEAE	**N**	**%**	**n**	**%**
Patients with TEAEs	377	75.2	103	62.8
Nausea	112	22.4	9	5.5
Insomnia	74	14.8	11	6.7
Dizziness	73	14.6	6	3.7
Headache	62	12.4	13	7.9
Vomiting	57	11.4	2	1.2
Nasopharyngitis	54	10.8	19	11.6
Somnolence	42	8.4	8	4.9
Fatigue	27	5.4	3	1.8
Decreased appetite	26	5.2	2	1.2
Accidental overdose	9	1.8	9	5.5
Fall	7	1.4	11	6.7

APTS = all patients treated set; PI = psychosocial intervention; TEAE = treatment-emergent adverse event.

Table 19. TEAEs With an Incidence of 5% or More, by Preferred Term (APTS): SENSE: Licensed Population

	Nalmefene + PI		Placebo + PI	
	n = 144		n = 42	
TEAE	**N**	**%**	**n**	**%**
Patients with TEAEs	112	77.8	26	61.9
Nausea	37	25.7	1	2.4
Dizziness	26	18.1	1	2.4
Insomnia	20	13.9	1	2.4
Vomiting	15	10.4	1	2.4
Headache	14	9.7	2	4.8
Nasopharyngitis	12	8.3	3	7.1
Hyperhidrosis	10	6.9	0	
Somnolence	10	6.9	3	7.1
Tachycardia	10	6.9	0	
Fatigue	9	6.3	2	4.8
Decreased appetite	8	5.6	0	
Accidental overdose	5	3.5	4	9.5
Fall	3	2.1	4	9.5
Contusion	2	1.4	3	7.1
Lower respiratory tract infection	0		3	7.1

APTS = all patients treated set; PI = psychosocial intervention; TEAE = treatment-emergent adverse event.

Table 20. TEAEs Leading to Withdrawal With an Incidence of 0.5% or More, by Preferred Term (APTS): ESENSE 1: Total Population

	Nalmefene + PI		Placebo + PI	
	n = 302		n = 296	
TEAE	**N**	**%**	**n**	**%**
Patients with TEAEs leading to withdrawal	69	22.8	22	7.4
Dizziness	16	5.3	0	
Nausea	16	5.3	0	
Fatigue	10	3.3	0	
Headache	9	3.0	0	
Sleep disorder	5	1.7	0	
Hyperhidrosis	4	1.3	0	
Alcoholism	3	1.0	0	
Insomnia	3	1.0	2	0.7
Restlessness	3	1.0	0	
Vomiting	3	1.0	1	0.3
Alcohol withdrawal syndrome	2	0.7	1	0.3
Decreased Interest	2	0.7	0	
Disturbance in attention	2	0.7	0	
Dry mouth	2	0.7	0	
Dysgeusia	2	0.7	0	
Feeling abnormal	2	0.7	0	
Muscle spasms	2	0.7	0	
Tremor	2	0.7	0	
Completed suicide	0		2	0.7

APTS = all patients treated set; PI = psychosocial intervention; TEAE = treatment-emergent adverse event.

Table 21. TEAEs Leading to Withdrawal With an Incidence of 0.5% or More, by Preferred Term (APTS): ESENSE 1: Licensed Population

	Nalmefene + PI		Placebo + PI	
	n = 179		n = 169	
TEAE	**N**	**%**	**n**	**%**
Patients with TEAEs leading to withdrawal	49	27.4	14	8.3
Nausea	14	7.8	0	
Dizziness	13	7.3	0	
Headache	7	3.9	0	
Fatigue	5	2.8	0	
Sleep disorder	5	2.8	0	
Hyperhidrosis	4	2.2	0	
Insomnia	3	1.7	1	0.6
Alcohol Withdrawal syndrome	2	1.1	1	0.6
Decreased Interest	2	1.1	0	
Disturbance in attention	2	1.1	0	
Dysgeusia	2	1.1	0	
Feeling abnormal	2	1.1	0	
Tremor	2	1.1	0	
Vomiting	2	1.1	1	0.6
Erectile dysfunction (SS)	1	0.9	0	
Abdominal pain	1	0.6	0	
Ageusia	1	0.6	0	
Agitation	1	0.6	0	
Alcohol poisoning	1	0.6	0	
Alcoholism	1	0.6	0	
Apathy	1	0.6	0	

	Nalmefene + PI		Placebo + PI	
	n = 179		n = 169	
TEAE	**N**	**%**	**n**	**%**
Arrhythmia	1	0.6	0	
Bipolar disorder	1	0.6	0	
Chills	1	0.6	0	
Convulsion	1	0.6	0	
Depressed level of consciousness	1	0.6	0	
Depression	1	0.6	0	
Depressive symptom	1	0.6	0	
Diabetes mellitus	1	0.6	0	
Dry mouth	1	0.6	0	
Epiglottic cyst	1	0.6	0	
Feeling cold	1	0.6	0	
Hearing impaired	1	0.6	0	
Hypomania	1	0.6	0	
Illusion	1	0.6	0	
Increased appetite	1	0.6	0	
Intervertebral disc protrusion	1	0.6	0	
Irritability	1	0.6	0	
Laryngeal oedema	1	0.6	0	
Malaise	1	0.6	0	
Metamorphopsia	1	0.6	0	
Muscle spasms	1	0.6	0	
Nervousness	1	0.6	0	
Non-cardiac chest pain	1	0.6	0	
Parosmia	1	0.6	0	

	Nalmefene + PI		Placebo + PI	
	n = 179		n = 169	
TEAE	**N**	**%**	**n**	**%**
Pyrexia	1	0.6	0	
Tinnitus	1	0.6	0	
Abdominal pain upper	0		1	0.6
Adjustment disorder	0		1	0.6
Arthralgia	0		1	0.6
Blood urea increased	0		1	0.6
Bradycardia	0		1	0.6
Cholecystitis acute	0		1	0.6
Completed suicide	0		1	0.6
Fall	0		1	0.6
Liver disorder	0		1	0.6
Major depression	0		1	0.6
Pneumothorax	0		1	0.6
Rash	0		1	0.6
Rash generalised	0		1	0.6
Rib fracture	0		1	0.6
Urinary tract infection	0		1	0.6

APTS = all patients treated set; PI = psychosocial intervention; SS = sex specific; TEAE = treatment-emergent adverse event.

Table 22. TEAEs Leading to Withdrawal With an Incidence of 0.5% or More, by Preferred Term (APTS): ESENSE 2: Total Population

	Nalmefene + PI		Placebo + PI	
	n = 341		n = 337	
TEAE	**N**	**%**	**n**	**%**
Patients with TEAEs leading to withdrawal	23	6.7	20	5.9
Dizziness	8	2.3	0	
Nausea	4	1.2	0	
Vomiting	3	0.9	0	
Anxiety	2	0.6	2	0.6
Insomnia	2	0.6	0	
Depression	1	0.3	5	1.5
Major depression	0		2	0.6

APTS = all patients treated set; PI = psychosocial intervention; TEAE = treatment-emergent adverse event.

Table 23. TEAEs Leading to Withdrawal With an Incidence of 0.5% or More, by Preferred Term (APTS): ESENSE 2: Licensed Population

	Nalmefene + PI		Placebo + PI	
	n = 152		n = 158	
TEAE	**N**	**%**	**n**	**%**
Patients with TEAEs leading to withdrawal	9	5.9	12	7.6
Dizziness	5	3.3	0	
Nausea	2	1.3	0	
Vomiting	2	1.3	0	
Abdominal pain	1	0.7	0	
Alcohol poisoning	1	0.7	1	0.6

	Nalmefene + PI		Placebo + PI	
	n = 152		n = 158	
TEAE	**N**	**%**	**n**	**%**
Asthenia	1	0.7	0	
Feeling abnormal	1	0.7	0	
Headache	1	0.7	0	
Insomnia	1	0.7	0	
Myocardial infarction	1	0.7	0	
Alcoholism	0		1	0.6
Anxiety	0		2	1.3
Depression	0		3	1.9
Drug toxicity	0		1	0.6
Epididymitis (SS)	0		1	0.9
Fibula fracture	0		1	0.6
Hepatitis alcoholic	0		1	0.6
Major depression	0		2	1.3
Pyothorax	0		1	0.6
Tibia fracture	0		1	0.6

APTS = all patients treated set; PI = psychosocial intervention; SS = sex specific; TEAE = treatment-emergent adverse event.

Table 24. TEAEs Leading to Withdrawal With an Incidence of 0.5% or More, by Preferred Term (APTS): SENSE: Total Population

	Nalmefene + PI		Placebo + PI	
	n = 501		n = 164	
TEAE	**n**	**%**	**n**	**%**
Patients with TEAEs leading to withdrawal	57	11.4	5	3.0

	Nalmefene + PI		Placebo + PI	
	n = 501		n = 164	
TEAE	**n**	**%**	**n**	**%**
Dizziness	12	2.4	0	
Nausea	10	2.0	0	
Disturbance in attention	5	1.0	0	
Insomnia	5	1.0	0	
Pregnancy (SS)	1	0.9	1	2.6
Alcohol withdrawal syndrome	4	0.8	1	0.6
Disorientation	4	0.8	0	
Fatigue	4	0.8	0	
Abdominal pain upper	3	0.6	0	
Decreased appetite	3	0.6	0	
Depression	3	0.6	1	0.6
Headache	3	0.6	0	
Hyperhidrosis	3	0.6	0	
Libido decreased	3	0.6	0	
Somnolence	3	0.6	0	
Vomiting	3	0.6	0	
Intentional overdose	1	0.2	1	0.6
Adjustment disorder with depressed mood	0		1	0.6
Haematemesis	0		1	0.6

APTS = all patients treated set; PI = psychosocial intervention; SS = sex specific; TEAE = treatment-emergent adverse event.

Table 25. TEAEs Leading to Withdrawal With an Incidence of 0.5% or More, by Preferred Term (APTS): SENSE: Licensed Population

	Nalmefene + PI		Placebo + PI	
	n = 144		n = 42	
TEAE	**n**	**%**	**n**	**%**
Patients with TEAEs leading to withdrawal	20	13.9	0	
Dizziness	7	4.9	0	
Disorientation	4	2.8	0	
Insomnia	3	2.1	0	
Decreased appetite	2	1.4	0	
Fatigue	2	1.4	0	
Hyperhidrosis	2	1.4	0	
Nausea	2	1.4	0	
Somnolence	2	1.4	0	
Abdominal pain upper	1	0.7	0	
Alcohol withdrawal syndrome	1	0.7	0	
Balance disorder	1	0.7	0	
Depressed level of consciousness	1	0.7	0	
Diarrhoea	1	0.7	0	
Diplopia	1	0.7	0	
Disturbance in attention	1	0.7	0	
Hallucination	1	0.7	0	
Headache	1	0.7	0	
Liver injury	1	0.7	0	
Nightmare	1	0.7	0	

APTS = all patients treated set; PI = psychosocial intervention; TEAE = treatment-emergent adverse event.

Table 26. SAEs With an Incidence of >1 Patient in Either Treatment Group, by Preferred Term (APTS): ESENSE 1: Total Population

	Nalmefene + PI		Placebo + PI	
	n = 302		n = 296	
SAE	**n**	**%**	**n**	**%**
Patients with TE SAEs	17	0.7	16	5.4
Alcoholism	2	0.3	2	0.7
Completed suicide	0		2	0.7
Convulsion	0		2	0.7

APTS = all patients treated set; PI = psychosocial intervention; SAE = serious adverse event; TE SAE = treatment-emergent serious adverse event.

Table 27. SAEs With an Incidence of >1 Patient in Either Treatment Group, by Preferred Term (APTS): ESENSE 1: Licensed Population

	Nalmefene + PI		Placebo + PI	
	n = 179		n = 169	
SAE	**n**	**%**	**n**	**%**
Patients with TE SAEs	11	6.1	5	3.0

APTS = all patients treated set; PI = psychosocial intervention; SAE = serious adverse event; TE SAE = treatment-emergent serious adverse event.

Table 28. SAEs With an Incidence of >1 Patient in Either Treatment Group, by Preferred Term (APTS): ESENSE 2: Total Population

	Nalmefene + PI		Placebo + PI	
	n = 341		n = 337	
SAE	**n**	**%**	**n**	**%**
Patients with TE SAEs	6	1.8	11	3.3
Intentional overdose	0		2	0.6

APTS = all patients treated set; PI = psychosocial intervention; SAE = serious adverse event; TE SAE = treatment-emergent serious adverse event.

Table 29. SAEs With an Incidence of >1 Patient in Either Treatment Group, by Preferred Term (APTS): ESENSE 2: Licensed Population

	Nalmefene + PI		Placebo + PI	
	n = 152		n = 158	
SAE	**n**	**%**	**n**	**%**
Patients with TE SAEs	4	2.6	7	4.4

APTS = all patients treated set; PI = psychosocial intervention; SAE = serious adverse event; TE SAE = treatment-emergent serious adverse event.

Table 30. SAEs With an Incidence of >1 Patient in Either Treatment Group, by Preferred Term (APTS): SENSE: Total Population

	Nalmefene + PI		Placebo + PI	
	n = 501		n = 164	
SAE	**n**	**%**	**n**	**%**
Patients with TE SAEs	34	6.8	8	4.9
Alcohol withdrawal syndrome	8	1.6	1	0.6
Atrial fibrillation	2	0.4	0	
Disorientation	2	0.4	0	
Fall	2	0.4	0	

APTS = all patients treated set; PI = psychosocial intervention; SAE = serious adverse event; TE SAE = treatment-emergent serious adverse event.

Table 31. SAEs With an Incidence of >1 Patient in Either Treatment Group, by Preferred Term (APTS): SENSE: Licensed Population

	Nalmefene + PI		Placebo + PI	
	n = 144		n = 42	
SAE	**n**	**%**	**n**	**%**
Patients with TE SAEs	11	7.6	1	2.4

APTS = all patients treated set; PI = psychosocial intervention; SAE = serious adverse event; TE SAE = treatment-emergent serious adverse event.

Table 32. Duration of Frequent Adverse Events (APTS): ESENSE 1: Total Population

	Duration (Median, Days)	
Adverse Event	**Nalmefene + PI**	**Placebo + PI**
APTS		
Dizziness	3.0	2.0
Nausea	5.0	2.5
Fatigue	7.0	18.0
Headache	3.0	2.0
Nasopharyngitis	9.0	12.0
Insomnia	6.5	18.5
Vomiting	1.0	2.5
Somnolence	11.0	2.5

APTS = all patients treated set; e = number of events; n = number of patients; PI = psychosocial intervention.

Table 33. Duration of Frequent Adverse Events (APTS): ESENSE 1: Licensed Population

	Duration (Median, Days)	
Adverse Event	**Nalmefene + PI**	**Placebo + PI**
APTS		
Dizziness	2.5	2.0
Nausea	5.0	2.5
Fatigue	6.0	24.5
Headache	3.0	2.0
Insomnia	7.0	
Nasopharyngitis	10.5	13.0
Vomiting	2.0	3.0
Somnolence	11.0	1.0

APTS = all patients treated set; e = number of events; n = number of patients; PI = psychosocial intervention.

Table 34. Duration of Frequent Adverse Events (APTS): ESENSE 2: Total Population

	Duration (Median, Days)	
Adverse Event	**Nalmefene + PI**	**Placebo + PI**
APTS		
Nausea	3.0	7.5
Dizziness	3.0	3.0
Insomnia	12.0	8.0
Headache	2.0	3.0
Nasopharyngitis	8.0	8.0
Vomiting	2.0	2.0
Fatigue	5.0	28.0
Somnolence	25.5	19.0

APTS = all patients treated set; PI = psychosocial intervention.

Table 35. Duration of Frequent Adverse Events (APTS): ESENSE 2: Licensed Population

	Duration (Median, Days)	
Adverse Event	**Nalmefene + PI**	**Placebo + PI**
APTS		
Insomnia	12.0	3.0
Nausea	11.0	11.0
Dizziness	3.0	2.0
Headache	3.0	3.0
Vomiting	2.0	2.0
Nasopharyngitis	7.5	6.0
Somnolence	11.0	19.0

	Duration (Median, Days)	
Adverse Event	**Nalmefene + PI**	**Placebo + PI**
Fatigue	34.5	22.5

APTS = all patients treated set; PI = psychosocial intervention.

Table 36. Duration of Frequent Adverse Events (APTS): SENSE: Total Population

	Duration (Median, Days)	
Adverse Event	**Nalmefene + PI**	**Placebo + PI**
APTS		
Nausea	2.0	2.0
Insomnia	4.0	6.0
Dizziness	3.0	2.5
Headache	2.0	2.0
Vomiting	1.0	1.5
Nasopharyngitis	7.0	8.0
Somnolence	1.0	3.0
Fatigue	6.0	3.0

APTS = all patients treated set; PI = psychosocial intervention.

Table 37. Duration of Frequent Adverse Events (APTS): SENSE: Licensed Population

	Duration (Median, Days)	
Adverse Event	**Nalmefene + PI**	**Placebo + PI**
APTS		
Nausea	3.0	3.0
Dizziness	3.0	15.0

	Duration (Median, Days)	
Adverse Event	**Nalmefene + PI**	**Placebo + PI**
Insomnia	5.0	3.0
Vomiting	1.0	1.0
Headache	2.5	15.5
Nasopharyngitis	8.0	8.0
Somnolence	1.5	7.0
Fatigue	10.0	

APTS = all patients treated set; PI = psychosocial intervention.

Compliance and Adherence

Table 38. Adherence to Medication (APTS): ESENSE 1: Total Population

	Nalmefene + PI	Placebo + PI
	n = 298	n = 293
Intake	**Mean %**	**Mean %**
IMP intake and drinking	35.8	48.7
No IMP intake and drinking	21.5	12.7
IMP intake and no drinking	11.8	15.2
No IMP intake and no drinking	30.5	23.2

APTS = all patients treated set; IMP= investigational medicinal product; PI = psychosocial intervention.

Table 39. Adherence to Medication (APTS): ESENSE 1: Licensed Population

	Nalmefene + PI	Placebo + PI
	n = 177	n = 167
Intake	**Mean %**	**Mean %**
IMP intake and drinking	41.6	60.6
No IMP intake and drinking	24.3	13.6
IMP intake and no drinking	9.2	12.6
No IMP intake and no drinking	24.3	13.1

APTS = all patients treated set; IMP= investigational medicinal product; PI = psychosocial intervention.

Table 40. Adherence to Medication (APTS): ESENSE 2: Total Population

	Nalmefene + PI	Placebo + PI
	n = 337	n = 333
Intake	**Mean %**	**Mean %**
IMP intake and drinking	37.1	40.3
No IMP intake and drinking	12.8	11.1
IMP intake and no drinking	19.9	24.8
No IMP intake and no drinking	30.1	23.8

APTS = all patients treated set; IMP= investigational medicinal product; PI = psychosocial intervention.

Table 41. Adherence to Medication (APTS): ESENSE 2: Licensed Population

	Nalmefene + PI	Placebo + PI
	n = 149	n = 156
Intake	**Mean %**	**Mean %**
IMP intake and drinking	49.7	55.1
No IMP intake and drinking	14.9	12.5
IMP intake and no drinking	15.6	16.3
No IMP intake and no drinking	19.6	16.2

APTS = all patients treated set; IMP= investigational medicinal product; PI = psychosocial intervention.

Table 42. Adherence to Medication (APTS): SENSE: Total Population

	Nalmefene + PI	Placebo + PI
	n = 499	n = 163
Intake	**Mean %**	**Mean %**
IMP intake and drinking	25.4	29.7
No IMP intake and drinking	7.4	4.6
IMP intake and no drinking	22.9	23.2
No IMP intake and no drinking	44.2	42.5

APTS = all patients treated set; IMP= investigational medicinal product; PI = psychosocial intervention.

Table 43. Adherence to Medication (APTS): SENSE: Licensed Population

	Nalmefene + PI	Placebo + PI
	n = 144	n = 42
Intake	**Mean %**	**Mean %**
IMP intake and drinking	37.2	50.8
No IMP intake and drinking	13.3	7.4
IMP intake and no drinking	14.8	10.9
No IMP intake and no drinking	34.3	30.9

APTS = all patients treated set; IMP= investigational medicinal product; PI = psychosocial intervention.