DRUG & ALCOHOL FINDINGS *Review analysis*

This entry is our analysis of a review or synthesis of research findings considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original review was not published by Findings; click Title to order a copy. Free reprints may be available from the authors – click prepared e-mail. Links to other documents. Hover over for notes. Click to highlight passage referred to. Unfold extra text. The Summary conveys the findings and views expressed in the review. Below is a commentary from Drug and Alcohol Findings.

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Risks and benefits of nalmefene in the treatment of adult alcohol dependence: a systematic literature review and meta-analysis of published and unpublished double-blind randomized controlled trials.

Palpacuer C., Laviolle B., Boussageon R. et al.

PLoS Medicine: 2015, 12(12), e1001924.

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'A pill for every ill' is the gist of the attacks levelled at nalmefene in the form of Selincro, a drug expected to extend the benefits of pharmacotherapy to drinkers not physically dependent or in need of detoxification – or for critics, to medicalise psychosocial dependence on shaky scientific grounds.

SUMMARY This summary is based on the journal editor's summary of the article.

To reduce harm alcohol-dependent individuals are usually advised to abstain, but transitioning to controlled, moderate drinking may also be helpful. Marketed under the trade name Selincro, the European Medicines Agency recently approved the medication nalmefene to help reduce alcohol consumption among alcohol-dependent men drinking over 60g (7.5 UK units) alcohol per day or women drinking over 40g (5 UK units). Nalmefene blocks the body's opioid receptors and reduces the craving for alcohol.

However, several expert bodies have concluded that nalmefene shows no benefit over naltrexone (an older treatment for alcohol dependence which also blocks opioid receptors) and do not recommend nalmefene's use for the treatment of dependent drinking.

To clarify these issues, the authors of the featured review investigated the risks and benefits of nalmefene in the treatment of alcohol dependence in adults by undertaking a systematic review and meta-analysis of double-blind, randomised controlled trials of nalmefene for this condition. A systematic review uses predefined criteria to identify all the research on a given topic. A meta-analysis combines the results of several studies. A double-blind randomised controlled trial compares outcomes in people chosen at random to receive different treatments without the researchers or the participants knowing who received which treatment until the end of the trial, an accepted way to ensure the outcomes are not due to pre-existing differences between people given the treatment versus those not, and that the results are due to the drug's effects, not due to expectations of patients or research staff about those effects.

The researchers identified five relevant trials which in total had involved 2567 participants, all of which compared the effects of nalmefene with a placebo (dummy drug). None of the trials specifically sampled participants drinking at the levels specified by the European Medicines Agency's approval.

Key points
From summary and commentary

Under the trade name Selincro, in 2013 the medication nalmefene was granted European marketing authorisation to help reduce drinking among dependent – but not physically dependent – high-risk drinkers.

The featured analysis found that the drug could not be shown to affect health and had only minor effects on drinking, or none if it was assumed patients missing at follow-ups had continued with or resumed pre-trial drinking.

Despite on balance positive results, shortcomings in the manufacturer's trials and the analyses on which authorisation was based have led to concerns that less severe forms of dependence are being inappropriately perhaps ineffectively medicalised, displacing psychosocial support.

Another concern is that there are reasons to believe that the parent drug, naltrexone, would be just as effective and much cheaper.

Main findings

In respect of the health outcomes examined in the meta-analysis, there were no significant differences between participants allocated to nalmefene versus placebo in death rates after six months or one year of treatment, in the quality of life at six months, or in a summary score indicating mental health at six months. Trials included in the meta-analysis did not report other health outcomes such as accidents.

Nalmefene patients drank heavily on one to two fewer days per month six months and one year after treatment started than participants allocated to a placebo, and their total alcohol consumption was slightly lower, all statistically significant differences. Measures of the severity of dependence and alcohol problems also improved more among the nalmefene patients. However, more people allocated to nalmefene than to a placebo withdrew from the studies, often for safety reasons. This and the high overall rate of attrition from the studies makes the findings vulnerable to bias because differences between the remaining two sets of patients can no longer be assumed to have been eliminated by random allocation. When the analysts accounted for patients lost to the studies by assuming they continued to drink as they did at the start of the trials, alcohol consumption outcomes were no longer significantly better among patients allocated to nalmefene. However, this was a worst-case-scenario 'conservative' assumption.

Deaths were too few to register a statistically significant difference, but were in favour of nalmefene, totalling to one out of 991 patients prescribed nalmefene and four out of 901 prescribed placebo.

The authors' conclusions

Among patients being treated for alcohol dependence, there is no high-grade evidence to support the use of nalmefene

Among patients being treated for alcohol dependence, there is no high-grade evidence to support the use of nalmefene to reduce alcohol-related harm, and little evidence that it reduces alcohol consumption. The value of nalmefene in the treatment of alcohol dependence is not established. Importantly, these findings reveal a lack of information on clinically relevant outcomes in the evidence that led to nalmefene's approval by the European Medicines Agency. It follows that they also call into question the decisions of this and other regulatory and advisory bodies which have approved nalmefene on the basis of the available evidence from randomised controlled trials, and highlight the need for further trials of the drug compared both to placebo and to naltrexone for the drinking disorders specified in the approvals.

> *The value of nalmefene in the treatment of alcohol dependence is not established*

No randomised trials were found which compared nalmefene versus placebo in the specific population for which the European authority approved Selincro – alcohol-dependent adults drinking over 60g a day for men or 40g for women. In this population, the only available data are pooled analyses derived from subgroups of the total samples in two or three of the trials, subgroups not specified before the results were known. The credibility of such analyses is usually low and they are not considered to confirm that the intervention is effective, only to identify avenues worth pursuing in trials designed from the start for this purpose.

No trials were found which compared nalmefene with another medication, but current evidence suggests there is little or no difference in efficacy in reducing heavy drinking between nalmefene and naltrexone. Although naltrexone is not authorised for reducing drinking as opposed to promoting abstinence, reduction is probably its main effect.

Clinicians must be aware that the value of nalmefene for the treatment of alcohol addiction is not established. At best, nalmefene has limited efficacy in reducing alcohol consumption.

FINDINGS COMMENTARY The story of Selincro's entrance in 2013 into the European market and its subsequent approval for NHS patients in the UK has important ramifications for how heavy drinking is regarded and (not) treated. To corroborate the following commentary we analysed the story in detail, and provide this detail in the form of background notes. Links to relevant passages in the notes are included in the commentary. The notes are also available at the end of this commentary in the form of headings with an 'eye-opener' link which you can click on to unfold the text under that heading.

'Not proven' only justifiable scientific verdict

Under the trade name Selincro, nalmefene's marketing authorisation by the European Medicines Agency in 2013 (▸ panel) paved the way to realising the hope that it will help tackle the bulk of dependent drinking lying below the iceberg-tip of physically dependent drinkers aiming for abstinence – and at the same time open up for Danish manufacturer Lundbeck a huge market previously all but closed to pharmaceutical solutions. The same prospect – but seen as a chimera – has also stimulated criticism from observers concerned at what in their eyes could prove an expensive and inappropriate medicalisation of lesser degrees of dependence based on unproven effectiveness.

Lundbeck may have carved out a potentially profitable marketing niche for Selincro, but this does not mean there is no substance to claims that the medication is effective and distinctive in helping dependent drinkers cut back. The questions on this front are twofold: whether in this role the drug has reliably been shown to be more effective than an inactive placebo; and if it has been, whether it has been shown more effective than established treatments, especially its less expensive parent drug naltrexone and 'talking' therapies, including inexpensive brief interventions.

European Medicines Agency authorisation

Selincro is used to help reduce alcohol consumption in adults with alcohol dependence who consume more than 60g [7.5 UK units] of alcohol per day for men or more than 40g [5 UK units] per day for women.

It should only be used ... in people who do not have physical withdrawal symptoms and who do not require immediate detoxification.

Selincro should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.

Selincro should be initiated only in patients who continue to have a high drinking-risk level two weeks after initial assessment.

Having reanalysed the available trials and been granted access to the data which underpinned authorisation, on both counts the featured analysis delivered a 'not proven' verdict, the trials neither offering statistically significant and reliable evidence of improved health nor (once patients lost to follow-up were accounted for) reduced drinking, while the absence of head-to-head trials against naltrexone left open whether the medication has the distinct advantages claimed for it.

Critical weaknesses in the case for Selincro are the unreliability of the analysis of outcomes from a selection of the patients in the trials which underpinned authorisation and subsequent approvals, and the apparently equivalent effects of naltrexone at a much cheaper price. Based on current evidence, the innovation in Selincro is not nalmefene nor the way it has been trialled in the treatment of alcohol dependence, but its market re-positioning by Lundbeck for a population of patients (not in need of detoxification, not physically dependent, wanting still to drink, probably not in specialist treatment) and for an objective (reducing consumption rather than sustaining abstinence) for which no medication had yet been specifically authorised. However, absence of reliable evidence might not mean there are no appreciable benefits, just that these have yet to be demonstrated. These conclusions are expanded on in the following text.

Missing patients undermine trial conclusions

Their findings led the authors of the featured review to question whether the drug's record warranted European authorisation. Highlighted as a major limitation of the Lundbeck-sponsored trials which led to authorisation was the substantial minority of patients lost to follow-up. Once this reaches high levels, there is no reliable way to be sure what the outcomes really were across all the patients in a trial.

Faced with this problem, the featured analysis assumed patients lost to follow-up were drinking the same as before joining the trials, an assumption which would be valid to the degree to which complete relapse was the reason for their non-response – conceivably the case for many drop-outs, but almost certainly not all. On this basis – one supported by the company and by the European Medicines Agency – it was estimated that placebo patients had reduced drinking by about the same as nalmefene patients, a result which must have been partly due to this pessimistic assumption having to be made for more nalmefene than placebo patients. But to base outcomes on just those patients who *did* complete final assessments would also have been unreliable.

Lundbeck's trials themselves depended on a different strategy to account for missing patients: using all the available

Lundbeck's trials themselves depended on a different strategy to account for missing patients: using all the available data including any interim follow-ups to estimate final outcomes. However, in the end this too relies on extrapolation from patients who complete final assessments, and also on the unlikely assumption that researchers have accounted for all the factors related both to drop-out and to the assessed outcomes. On this basis, relative to placebo the primary measures of drinking – total consumption and heavy drinking days at the 24-week follow-ups – had been reduced to a statistically significant degree by nalmefene in three of the tests made across the three studies, but not in another three. Across the three trials, most ways of assessing the primary drinking outcomes left nalmefene without a statistically significant advantage over a placebo.

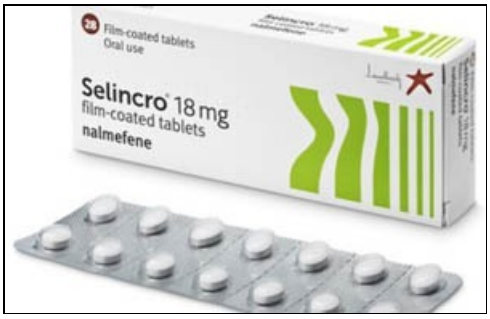
Analysis selects patients among whom "the benefit of Selincro would be greatest"

Faced with patchily positive results, Lundbeck and their research associates conducted 'sub-sample' analyses which excluded over half the participants in the trials, including medium-risk drinkers and those at higher risk who even before treatment started had rapidly remitted to a lower risk level on joining the trials. From an earlier analysis and because this selection was made after trial results were in, it would have been known that the rapid remitters tended to stay that way. The effect was to exclude patients who left any treatment little to improve on. What remained were a higher risk sub-sample who remained at high risk when nalmefene treatment started. Among these patients, the drug had greater scope to prove it could reduce drinking, and the results were more consistently positive, but at the cost of reliability.

Sub-sampling deprived the resulting findings of the assurance of a level playing field created by randomisation of the original samples, and left the outcomes vulnerable to manipulation and bias – the reasons why they are considered suitable only for suggesting possibilities, not proving effectiveness. Particularly worrying is the statement in the European Medicines Agency's assessment that sub-sampling had been "proposed" by Lundbeck "in order to define a population where the benefit of Selincro would be greatest"; it seems that not just the effect but the intention was to find a way of dividing the sample which would be advantageous to Selincro. Sub-sampling also left in the analysis a small and probably atypical set of drinkers, recruited on average just once every four months at each research site. Together with the multiple reasons for excluding applicants from the trials, it meant the results could not be relied on as an indication of nalmefene's likely impact among the generality of drinkers considered eligible for the medication.

Better than the alternatives?

Lundbeck's trials and European authorisation were based on assessment of whether nalmefene was better than (pharmacologically) nothing in the form of an inactive placebo when both were accompanied by a low-intensity psychosocial programme whose main aim was to enhance compliance with treatment. But that is not enough to justify publicly funding the drug's supply to National Health Service patients. To capitalise on the authority to market Selincro, its manufacturers had to persuade authorities like Britain's National Institute for Health and Care Excellence (NICE) that it offered acceptable levels of health-improving and lifesaving benefit per £ of public resources, and that either there were no alternatives, or that these offered less net benefit.



What the controversy is all about: Lundbeck-branded Selincro

The comparator in Lundbeck's trials amounted to a psychosocial programme whose main aim was to get patients to take inactive pills – not a real-world alternative to nalmefene. More realistic alternatives were an active medication accompanied by psychosocial support, or a standalone psychosocial therapy focused on reducing drinking and related risks.

Pharmacologically, the obvious alternative was naltrexone. On that front, the company's argument was that the remit specified in its approvals meant it was not an alternative for the patients and uses envisaged for Selincro. Despite not being licensed for Selincro's role, in fact naltrexone has successfully been used for essentially the same types of drinkers and taken in the same way – 'as needed' in anticipation of drinking. That naltrexone has not been specifically authorised for these purposes seems mainly down to no pharmaceutical company having pursued such authorisation; little would be gained from promoting new uses for a medication exposed to generic competition from products no longer protected by patents.

On psychosocial alternatives, the argument was that in practice these were often similar to the approach whose effects nalmefene augmented in the Lundbeck trials. However, the comparator in the original remit for the decision to be made by NICE was not a brief package to promote the taking of inactive pills, but the fully-fledged, standalone psychological and social therapies NICE had previously recommended for the types of drinkers targeted by Selincro.

In respect both of naltrexone and psychosocial therapies, no direct comparisons were available in the form of studies which had randomly allocated patients to nalmefene versus these alternatives. It left a crucial blank in the data available to the national authorities which held the keys to releasing public funds for Selincro. In the end, they largely based their decisions on the data they did have from Lundbeck: that according to an analysis unsuited to demonstrating effectiveness, among a sub-sample of high risk and perhaps also highly atypical drinkers, paired with a basic psychosocial programme intended to get patients to take pills as directed, it was slightly better if those pills were an active medication in the form of nalmefene than an inactive placebo.

Unreliable foundation for authorisation

On this unreliable foundation substantially rested the case for allowing the company to market Selincro in Europe and subsequent decisions to mandate Britain's National Health Service to make it available to patients. In self-justifying circles, during the European authorisation process Lundbeck conducted the sub-sampling analysis in order to leave nalmefene performing more convincingly than in the full samples, which in turn justified authorisation for these kinds of drinkers, which then justified a published analysis focused on these types of drinkers, all of which justified cost-effectiveness analyses (1 2) limited to this sub-sample, leading to the decision that the NHS must make it available for those purposes – a chain of decisions, each link of which retained the vulnerability to bias and questionable applicability to the generality of patients introduced by the initial sub-sampling.

> *Each link in the chain of approvals retained the vulnerability to bias of the initial analysis*

For Selincro and for Lundbeck, the unsatisfactory result is that relative both to a placebo and to alternative treatments, an unproven verdict is the only scientifically defensible one. Even assuming a real effect, this generally small advantage will have been bought at the cost of the unpleasant side effects experienced by a substantial minority

small advantage will have been bought at the cost of the unpleasant side effects experienced by a substantial minority of patients. In the three Lundbeck-funded trials on which European authorisation was based, nausea afflicted around a fifth to a quarter and vomiting from 6% to 18%, incidents much rarer on placebos.

Aggravating uncertainties about the science is the deep involvement of the manufacturers in all the main trials on which marketing authorisation and subsequent NICE approval were based. For Lundbeck, it was very important to profit from this new product as revenue fell from older products whose patents had expired, leaving them exposed to generic competition. Highlighting these "vested interests" has been a feature of criticisms of how marketing and approval decisions were made, fuelled partly by concern that heavy drinking will become medicalised rather than dealt with by psychosocial support or self-help, and that in particular the space in public policy hard-won for brief interventions will become occupied by a relatively costly medication. For people who see dependent drinking as fundamentally a psychological and social problem, it represents an unwelcome extension down the severity range of an opposing vision of the condition as due to neurochemical processes correctable by a drug which targets opiate receptors in the brain.

> *The opposing risk is of throwing the baby out as well as the bathwater*

The opposing risk is of throwing the baby out as well as the bathwater – the risk that despite scientific imperfections and strongly vested interests, Selincro really can help fill an important gap in the reduction of alcohol-related harm. Absence of reliable evidence might not mean there are no appreciable benefits, just that these have yet to be demonstrated. Randomised trials are not easy to conduct; imperfections are inevitable, as usually is questionable applicability to the intended population. Failing to implement interventions found effective in these trials risks depriving sufferers of valid sources of relief. Some of Selincro's marketing advantages for Lundbeck are also reasons why dependent drinkers who do not see themselves as 'alcoholics' in need of treatment might be prepared to give it a try. Small effects there may be, but if they are real and are multiplied over many thousands of people drinking at risky levels, they could cumulate to a worthwhile public health gain.

Fears too about a retrograde influence of the introduction of Selincro may not materialise. Though it could happen, there is no inevitability about Selincro gaining ground at the cost of brief interventions, which are targeted mainly at people not seeking treatment, nor at the cost of psychosocial therapies for treatment seekers, which perhaps appeal to a different kind of patient treated in different circumstances to that envisaged for Selincro. Nor is the fact that nalmefene is a medication necessarily a challenge to psychological understandings of addiction. Though the manufacturers portray alcohol dependence as a brain disease caused by repeated drinking, the proposed mechanism of action of nalmefene – diminishing the rewarding effects of alcohol – is compatible with understandings of dependence as an acquired habit, theories which underpin the cognitive-behavioural approaches popular in the addictions. In this scenario, nalmefene just makes it easier to lose the habit. A bonus for many will be that the medication's approvals explicitly endorse controlled drinking as a treatment objective, a step towards extending the legitimacy of this contested route out of dependent drinking.

These themes in the story of what has become a highly controversial product attracting great expectations for extending health gains and correspondingly major criticism are expanded on under the headings below, which duplicate the background notes. For technical reasons, in the text below internal links to parts of the text which are still hidden will not work, but these links should work as expected in the background notes file.

Thanks for their comments on this entry in draft to research author Florian Naudet of Stanford University in the USA, and to Matt Stevenson of the University of Sheffield in England, Alain Braillon of the Department of Medicine at University Hospital in Amiens, France, and James Morris of the Alcohol Academy based in England. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

UNFOLDABLE EXTENDED TEXT. Click headings to reveal text

The Lundbeck trials

Lundbeck trial 1

Lundbeck trial 2

Trials 1 and 2

Lundbeck trial 3

Trials 1, 2 and 3

Other trials

European authorisation

Could naltrexone play Selincro's role more cheaply?

Clinically insignificant differences

Commercially significant differences

Naltrexone trials suggest nalmefene-type impacts

Questionable 'first indication that nalmefene is superior'

Naltrexone and nalmefene go head to head

UK follows the European decision

NICE recommends Selincro

Cost-effectiveness relative to psychosocial care

Cost-effectiveness relative to naltrexone

NICE reaches its decision

Last revised 01 September 2016. First uploaded 10 August 2016

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MATRIX CELL 2016 Alcohol Matrix cell A2: Interventions; Generic and cross-cutting issues

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STUDY 2010 A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence

REVIEW 2014 Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

DRUG & ALCOHOL FINDINGS *Background notes*

BACKGROUND NOTES: RISKS AND BENEFITS OF NALMEFENE IN THE TREATMENT OF ADULT ALCOHOL DEPENDENCE: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS OF PUBLISHED AND UNPUBLISHED DOUBLE-BLIND RANDOMIZED CONTROLLED TRIALS

Return to main entry

The Lundbeck trials

Three trials underpinned the success of Lundbeck's application to market Selincro in Europe and of the company's submissions to NICE and other authorities which act as gateways to the National Health Service market.

Each trial had been funded by Lundbeck, which also had a direct hand in their design, data collection, data analysis, and the interpretation of the data. Study authors not actually employed by Lundbeck had all in various ways benefited from the company. The situation stimulated reviewers to comment, "Alcohol problems are complex, and require evidence unbiased by vested interests." They were referring to the so-called 'researcher allegiance' effect – a concern in several medical and social research areas (1 2 3) where programme developers and other researchers with an interest in the intervention's success have been found to record more positive findings than fully independent researchers.

All three trials shared features which undermined their reliability as indications of nalmefene's impacts among the generality of intended patients – important, because Selincro's main selling point is its supposed ability to attract and aid the wide sweep of non-physically dependent heavy drinkers who do not want to stop altogether, not just its ability to aid individuals who join trials.

The trials excluded applicants for multiple reasons in ways likely to lead to relatively stable and healthy samples compliant with treatment. Partly for this reason, the studies seem to have recruited very few participants given the number of recruitment sites and methods used to recruit them. Typical exclusion criteria can eliminate the great majority of treatment-seeking drinkers from trials. Any medication will only exert a pharmacological effect if taken, so in turn these exclusions risked creating an unrealistically positive impression of how the drug would perform across all potential patients.

The process of sifting potential participants not only impedes generalisation of the findings to all the drinkers Selincro might be prescribed to, but can undermine the reliability of the findings for those who did join the trials. Arguably too, the multiple chances given nalmefene to prove effective should have been adjusted for by raising the barrier to statistical significance. But the most obvious flaws – explained further below – were that the researchers were unable to re-assess many participants at later follow-ups, and that the most influential findings derived from analyses not planned in advance.

With a high drop-out rate, the assumptions made about missing patients proved critical to the findings. Drop-out at this level undermines the reliability of the findings even among participants who *did* complete follow-up assessments, because the even playing field assured by randomisation may have become tilted. Generalising the results across all the patients in a study creates a further detriment to reliability, because non-respondents may differ in important ways from those who did respond.

The strategy the studies prioritised was to use all the available data, including any interim follow-ups, to estimate final outcomes. In the end this relies on extrapolation from patients who complete final assessments, and on the unlikely assumption that the researchers had taken into account all the factors related both to drop out and to the assessed outcomes.

On this basis, relative to placebo the primary measures of drinking – total consumption and heavy drinking days at the 24-week follow-ups – were reduced to a statistically significant degree by nalmefene in three of the tests made across the three studies, but not in another three. When it was assumed that patients carried on drinking as they had the last time they were assessed, the tally rose to four significant tests out of six. But when – as in the featured analysis – it was assumed that missing patients had relapsed to (or continued at) their pre-trial drinking levels, none of the tests proved statistically significant.

The last variant is significant because Lundbeck staff and analysts commissioned by the company have endorsed a very similar assumption. A return to pre-trial drinking among missing participants was also the assumption the European Medicines Agency's experts recommended be used as the basis for public information on the medication. If this is indeed the most suitable assumption, it means none of Lundbeck's trials showed a single statistically significant effect on the primary measures of drinking chosen in advance for the studies. Across all the methods for assessing primary drinking outcomes at 24-weeks shared by at least two of the three trials, 15 of 34 were significantly in favour of nalmefene; most were not.

Faced with patchy results, Lundbeck and their research associates excluded over half the samples to focus on a high-risk sub-sample of drinkers (averaging at least 7.5 UK units a day for men and 5 for women) who did not respond to joining the trials by de-escalating their drinking to a lower risk level even before treatment started. Among these drinkers, nalmefene had greater scope to prove it could reduce drinking, and the results were more consistently positive – both primary measures of drinking significantly reduced across the two main studies, and one of the measures in the third study. It was, however, a result extracted at the cost of reliability. The analysis deprived the resulting findings of the reassurance of the level playing field created by randomisation of the original samples, and left them vulnerable to manipulation and bias. At worst, it enables analysts to capitalise on the fact that samples can be sub-sampled in any number of ways until one (perhaps purely by chance) results in a significant finding. For these reasons, analyses which after the results are known slice up randomised samples to test if certain types of patients benefited are considered suitable only for throwing up hypotheses to be tested in a study designed for that purpose. In this case the sub-sampling crierion excluded patients for whom nalmefene was known from the European approval process to have made no difference, leaving in a sub-sample intended to show Selincro at its most effective. Sub-sampling also left in the analysis a small and probably atypical set of drinkers, recruited on average just once every four months at each research site.

The reasoning for slicing the sample this way was that the excluded patients "may represent excessive drinkers who

The reasoning for slicing the sample this way was that the excluded patients "may represent excessive drinkers who after making the decision to seek help can reduce their drinking with minimal intervention." But the risk level cut-off on which so much hinged was never intended to be used in this way. Rather than a clinical tool for assessing patients for treatment, it derived from World Health Organization recommendations for epidemiologists comparing drinking within and across countries. Even in this role, the levels are based on "drinking on a given day" and indicate the amounts which increase risk of 'acute' adverse effects related to intoxication. They "must be clearly distinguished from those which apply to typical daily drinking i.e. average intake of alcohol across all days which will usually be a lower figure," said the World Health Organization's experts. Yet in the Lundbeck trials, these levels *were* applied to average daily drinking, distancing them further from any accepted indication of risk levels warranting treatment or certain kinds of treatment.

Without an overriding clinical rationale, there seems no reason why the slicing could not have been done differently – for example, the second trial's option of excluding patients who at the start of treatment would no longer have qualified for the trial, selecting all drinkers at high risk and above at the start of treatment, selecting only very high risk drinkers, altering the cut-off to a different consumption level, choosing a proportion of heavy drinking days as the criterion, or instead a certain severity of dependence.

A key shared feature of the trials was the brief, low-intensity BRENDA psychosocial support programme, whose main aim is to motivate and enable patients to take their medication as prescribed. When authorities came to consider the applicability of the results to UK practice, it became clear that BRENDA fell between two stools: it did not have the focus in its aims nor the intensity or extensity recommended for the standalone psychosocial therapies against which nalmefene's effectiveness was compared; yet it was *too* structured and extensive to be well implemented by GPs, the expected primary prescribers of nalmefene. The result was to raise questions about nalmefene's performance relative to recommended practice, and whether its trials record would be replicated when it was coupled with typical primary care clinical support.

Set against these cautions was the general consistency of greater (if not significantly greater) drinking reductions on nalmefene than placebo, and the fact that often this was apparent early in the follow-up period when nearly all the patients who started the trials were still contributing data. It also seems that most patients who left at least the first two trials were at the time on a stable or decreasing trajectory in their drinking. This does not mean all stayed that way, but is a reason why assuming complete relapse to pre-study drinking levels – the assumption which left not a single statistically significant effect on primary drinking measures – might be too pessimistic. The sub-sampling method, though one of many which might have made sense, is defensible as a way of narrowing the samples to the kind of drinkers most likely to be considered for pharmacotherapy.

After making these general points about all three trials, below we detail the Lundbeck trials and other trials which shed light on nalmefene's potential to reduce drinking and with it associated harm.

Lundbeck trial 1

The first of what the European Medicines Agency saw as the two "pivotal" trials funded by Lundbeck had recruited alcohol-dependent patients at clinics in four northern-European countries via normal attendances and replies to advertisements. Over the previous four weeks, each had to have averaged at least the World Health Organization's medium-risk drinking level – 40g a day for men and 20g for women – and on at least six of those days stepped up to WHO's high-risk level (an additional 20g), yet at the screening visit they had to be sober and not experiencing withdrawal symptoms severe enough to warrant medically assisted detoxification. In practice, on average they had drank at or above high-risk levels on 20 of the previous 28 days and averaged about 85g (nearly 11 UK units) of alcohol a day.

After one or two weeks applicants who qualified for and agreed to join the study were allocated at random for 24 weeks either to nalmefene or to an identical-looking but inactive placebo. They were instructed to take up to one tablet a day 'as-needed', preferably between one and two hours before they felt they might start drinking. In addition, they were offered (variously said to have lasted from 10 minutes to half an hour) sessions with their doctors to enhance motivation and compliance with treatment, sessions usually four weeks apart.

The first serious question over the trial is the representativeness of the drinkers it recruited. At 39 sites and over 15 months, 770 applicants completed screening to see if they qualified for the trial – fewer than one every month at each site, among which were clinics in major cities like Berlin, Hamburg and Stockholm. In the end, 604 applicants were randomly allocated to nalmefene or placebo; all but one was categorised as Caucasian. Other than smoking, to join the study applicants had to be free of drug use or serious mental health problems, not taking a range of medications, and not recently in treatment for their drinking. Among the long list of criteria was the researcher's "opinion" that the applicant was "unlikely to comply with the protocol or is unsuitable for any reason". Several other criteria were meant to or would probably select out applicants less likely to comply both with the study and with treatment.

If the patients started off being highly selected, by the end they were even more so. Across both sets of patients allocated either to nalmefene or placebo, those who provided final follow-up data on their drinking amounted to about nine per site or just over one every two months at each of the locations.

Of the 604 randomly allocated patients, 579 both took at least some medication and completed at least one follow-up assessment, so were included in the outcomes analyses. The main outcomes were based on drinking levels assessed at the end of the medication period, but these assessments were available for just 60% of the drinkers who started the trial and 63% of those included in the outcome analyses. For the remainder, final drinking levels had to be estimated, estimates which despite their sophistication relied on extrapolations from patients who did supply final follow-up data.

A low overall completion rate was made worse by the greater drop-out on nalmefene: only 152 of these patients contributed final follow-up data on their drinking, meaning that the primary drinking outcomes could directly be assessed on just half those who started the trial.

Based on the 6 in 10 patients who supplied this data, from their pre-trial screening levels nalmefene patients were at the end of the 24 weeks drinking on average 51g of alcohol less a day but placebo patients just 40g less, a statistically significant difference amounting to an extra reduction of 11g or nearly one and a half UK units. This primary analysis was supplemented by different ways of accounting for patients who missed the final follow-up. Generally these also left a statistically significant extra reduction in average consumption among nalmefene patients. An exception was the assumption that missing patients had continued to drink or relapsed to drinking at their pre-trial levels. On this basis it was estimated that drinking reductions were about the same, a result which must have been due to this assumption having to be made for many more nalmefene patients.

Similar results were reached for heavy drinking days, though effects were modest – an extra 2.3 days fewer per 28 days starting from a base of around 19.5 days, an extra reduction of 12%. Proportions of patients who moved down drinking risk levels were also generally greater on nalmefene than placebo, though a no-movement assumption for

drinking risk levels were also generally greater on nalmefene than placebo, though a no-movement assumption for missing patients left placebo patients doing significantly *better* than those allocated to nalmefene. Only an unplanned and therefore unreliable extrapolation from known to unknown data generated a statistically significant difference in the expected direction.

Lundbeck trial 2

A second trial from essentially the same research team used the same methodology, but recruited from seven countries from Western and Eastern Europe, including from the south, Italy, Portugal and Spain. As in trial 1, there are reasons to question the representativeness of the drinkers recruited to the trial and even more so those who supplied final follow-up data, and the criteria for excluding applicants from the trial probably left relatively stable and committed patients who might create an unrealistically positive impression of how the drug would perform in routine practice.

Over 17 months, at the 57 sites 941 patients were screened for eligibility for the study and 718 randomly allocated to as-needed nalmefene or placebo, under one a month per site. Of the 718, 655 both took at least some medication and completed at least one follow-up assessment, so were included in the outcomes analyses. Before screening they were averaging about 91g or 11 to 12 UK units of alcohol a day. Just 61% of the patients who started the study supplied the 24-week outcome data on which findings were based. Compared to trial 1, fewer nalmefene patients left after reactions such as nausea and dizziness, and about the same proportion dropped out whether prescribed nalmefene or placebo.

Except for extra reductions in the proportion of heavy drinking days, the results were unconvincing. Of six ways of analysing whether on average nalmefene patients had reduced consumption more than those prescribed a placebo, only two generated a statistically significant extra reduction. The primary analysis was based on the 6 in 10 patients who supplied baseline and final follow-up data. From their pre-trial values, nalmefene patients were at the end of the 24 weeks drinking on average 59g of alcohol less a day and placebo patients 54g less, a small and non-significant difference. Assuming that patients who missed the final follow-up had maintained their last-known drinking level generated a statistically significant 6g a day extra reduction among the nalmefene patients, but assuming they had continued to drink at or relapsed to pre-trial drinking left an insignificant 3g difference. Of the two ways which assumed missing patients drank similarly to placebo patients, the most sophisticated also left just an insignificant 3g difference.

Findings on heavy drinking days were more consistently significant and in favour of nalmefene, but effects were modest – starting from a base of around 19 days, an extra 9% or 1.7 days fewer per 28 days. Of the five tests of whether more nalmefene patients de-escalated drinking risk level categories, just one was statistically significant, and assuming missing patients had not improved left placebo patients doing slightly and non-significantly *better* than nalmefene patients.

In the one or two weeks between joining the trial and starting treatment, a third of the patients had reduced their drinking so much that they would no longer have qualified for the trial, either now drinking at low risk levels or not drinking heavily on fewer than six of the past 28 days. Before taking a single pill, they had on average reduced their drinking from around 81g to less than 20g a day, and had then carried on drinking little regardless of whether allocated to placebo or nalmefene. In contrast, based on just the patients who provided these measures, the remaining two-thirds of patients made only minor reductions before starting treatment and then made small but consistently and significantly greater reductions in average consumption and heavy drinking days if they had been allocated to nalmefene. For the authors this was evidence "confirming the pharmacological effects of nalmefene relative to placebo in this important subpopulation" – an over-positive conclusion, because sub-sample analyses of this kind mounted after trial data are in are considered suitable only for suggesting possibilities worth testing in a study designed for this purpose.

Trials 1 and 2

Later a somewhat different way of slicing up the samples was applied to pooled results from trials 1 and 2. It suggested that on average the only beneficiaries from nalmefene were high-risk drinkers (exceeding the equivalent at least 7.5 UK units a day for men and 5 for women) who did not respond to joining the trial by de-escalating their drinking – the drinkers for whom on the basis of this analysis the European Medicines Agency was later to authorise Selincro. Despite robust and consistent findings, again this result was suspect because it derived from analyses conducted after trial results were known, and in particular after it was known in trial 2 that a similar division of the sample excluded patients among whom nalmefene had no effect, leaving a sub-sample in which effects were more noticeable. It seems likely that many ineffective interventions could be made to look effective by finding a way to exclude parts of the sample who did not respond to the treatment. In this case too, the sub-sampling criterion was justified on the grounds that it resulted in a sub-sample which closely duplicated the patients for whom European authorisation had been granted – a circular process since the granting had been based on the same analysis. Given the wide and lengthy recruitment process for the trials, this analysis also rested on a small and possibly atypical set of drinkers. They had been recruited at in total 96 European sites, averaging just four at each site over 15 or 17 months, about one every four months.

For this sub-sampling exercise, 667 patients were selected who had started the trial at high risk or above drinking levels (for men averaging at least 60g a day, women 40g) and were still at that level when a week or two later they started treatment. This excluded not just the medium-risk drinkers, but also higher risk drinkers who did not rapidly remit to a lower level before starting treatment. Once patients who never took any pills were excluded, it left just under half the patients randomly allocated to nalmefene or placebo.

The sub-sampled, high-risk patients were averaging about 106g alcohol a day or just over 13 UK units, but most were not living alone and most too not unemployed, and only a third had previously been treated for drinking problems. This sub-sample was narrowed slightly further to the 641 patients who had both taken some of the prescribed pills and supplied some follow-up data. Of these, numbers supplying data on their drinking fell over the course of the trials to 413 at the end of the 24 weeks of the medication phases, amounting to 62% of the sub-sampled high-risk drinkers and under a third of all randomised participants.

It was estimated that offered nalmefene, this sub-sample had by the end of the 24 weeks reduced drinking by on average 66g a day compared to 51g for placebo patients, a statistically significant extra reduction of 14g a day on nalmefene or nearly 2 UK units. The other half of patients (with lower risk drinking at the start of the trial and/or the start of treatment) substantially reduced their drinking before treatment started, and then essentially maintained this reduction to almost exactly the same degree whether offered nalmefene or placebo.

A similar picture was seen with the number of heavy drinking days. From around 16 in 28 days, by the end of the 24 weeks the tally had fallen by 9.4 days on placebo but 12.6 on nalmefene, and extra reduction of 3.2 days in the last 28-day period, standardising to a small to medium 'effect size' of 0.33, results confirmed by liver function tests indicative of regular heavy drinking.

Another report on the same 667 patients found nalmefene led to greater improvements than placebo in health-related

Another report on the same 667 patients found nalmefene led to greater improvements than placebo in health-related quality of life and in adverse consequences of drinking, though again at the 24-week follow-up these results derived from only around 60% of the sub-sampled patients.

Pooled results from all the patients in the two trials were also used to examine the feasibility of the as-needed regimen. Nalmefene patients took the drug on 75% of the days on which they drank but just 38% of their abstinent days, and the more they drank before the start of treatment and in the first month, the more they took the medication – figures consistent with the medication generally being used as intended to moderate drinking.

Lundbeck trial 3

Also available to the European Medicines Agency were the results of a year-long trial from the authors of the previous two trials and of similar design. Despite offering treatment for 52 weeks, the primary measures of drinking reductions were to relate to the first 24 weeks and only secondarily to the end of the 52 weeks. As in previous trials, participants had to have drunk heavily on at least six of the past 28 days, and during that time not been abstinent for two weeks in a row, but this time they did not have to exceed any particular average consumption. However, only the 84% who as in previous trials consumed at or above WHO's medium-risk drinking level – 40g a day for men and 20g for women – were included in the outcome analyses, though only if they had also taken some medication and completed at least one follow-up assessment.

Over seven months 841 patients were screened and 675 randomly allocated to placebo or nalmefene at 60 sites mainly in Eastern Europe, but also at sites in five major UK urban areas – the first UK sampling. Recruitment averaged one or two patients per month at each site. Most were employed and most too living with someone else. The 552 included in the outcome analyses averaged 75g alcohol or just over 9 UK units a day before joining the study.

Whether prescribed nalmefene or placebo, on average patients substantially curbed their drinking, but by the study's primary yardstick, at the 24-week point nalmefene had made no statistically significant extra impact either on average consumption or on the proportion of days during which patients exceeded WHO's high-risk drinking level – 60g a day for men and 40g for women.

Though results at 24 weeks were disappointing, there had been significant, small extra reductions at earlier and later follow-ups, and on both measures these were evident at the end of the trial. Based on the 355 patients who had supplied this data, the extra nalmefene-versus-placebo reductions during the final four of the 52 weeks of the trial amounted to 6.5g a day less drinking and 1.6 fewer heavy-drinking days. This final follow-up, which yielded the only pre-planned indication that nalmefene had reduced drinking, was completed by 64% of the patients included in the outcome analyses, amounting to 53% of the patients originally allocated to nalmefene or placebo. Losing nearly half the sample creates considerable scope for tilting the level playing field intended to be assured by randomisation. At the 24-week point, nearly all the ways of taking into account patients who did not supply follow-up data had left the significance level of the reductions further eroded. Had these analyses been done for the final follow-up, effects might have been reduced to non-significance.

Alerted by sub-sampling results from the first two trials, the analysts mounted a similar unplanned analysis of the 183 patients who had started the trial at high risk or above drinking levels (for men averaging at least 60g a day, women 40g) and who were still at that level one or two weeks later when they started treatment. Based on data supplied by 134 of these patients, this time at the 24-week point there was a statistically significant extra reduction in drinking among nalmefene patients amounting to an extra 15g a day. By the 52-week follow-up this had increased slightly to 17g, over 2 UK units, though at this point just 109 patients supplied data. It was only at the 52-week point that the extra reduction in heavy drinking days reached significance. Other ways of adjusting for missing data might have rendered these findings insignificant, as might adjusting for the multiple chances given nalmefene to prove its worth. Most importantly, the analysis shares the weakness of the sub-sampling in the previous trials of not being planned in advance of the data being known.

Trials 1, 2 and 3

Another Lundbeck-funded report has focused on the patients who started the three trials at high-risk or above drinking levels and were still at high risk one or two weeks later when they started treatment. Three of the five authors were Lundbeck staff and another had been financially supported by the company and was on the "nalmefene board at the time when the manuscript was conceptualised".

Based on the reduction in deaths to be expected if these drinkers remit to abstinence or low-risk drinking, and the unlikely assumption that nalmefene's effects persist for three and a half years, the estimate was made that over nine years there would be 8% or 9% (depending on how missing data was accounted for) fewer deaths if patients were prescribed nalmefene versus placebo.

These analyses retain the weaknesses of the unplanned sub-sampling of the source trials, and the report did not include an analysis based on the assumption that missing patients continued to drink or relapsed to drinking at their pre-trial levels, in another context, a methodology supported by Lundbeck staff and by analysts commissioned by the company.

Real deaths in Lunbeck's nalmefene trials have been too few to be sure of its impacts. Based on the three trials, over six months the featured analysis did find deaths fewer on nalmefene, but not to a significant degree; over this time scale and with samples selected for relative health and social stability, the numbers were bound to be small. Over the full 52 weeks of the longer term trial there was just one death – of a passenger in a car accident – which could neither be attributed to the medication nor to any failure to curb drinking.

Other trials

While the three Lundbeck trials were the ones which persuaded the European Medicines Agency to authorise the marketing of Selincro, what seems the first randomised trial had been published nearly 20 years earlier in 1994. It was funded by the US government's alcohol agency and aided by the company which presumably then manufactured the drug.

This tiny pilot study involved just 21 patients in the USA described as mildly or moderately dependent on alcohol and drinking on average about 120g or 15 UK units on each of the three to four days a week they drank. They had responded to study ads and been randomly allocated to 12 weeks of 40mg nalmefene (twice the dose in the Lundbeck trials), 10mg nalmefene, or a placebo, all split into two daily tablets to be taken routinely rather than 'as-needed'. No psychosocial support was directly provided, but patients were encouraged to seek further help; few did. Only on the 40mg dose did the seven patients experience a significantly lower rate of relapse to heavy drinking and a greater

increase in the number of abstinent days per week than the other 14 patients

increase in the number of abstinent days per week than the other 14 patients.

Encouraged by these results, at a Miami alcohol clinic the authors mounted a larger trial which randomly allocated 105 patients whose drinking was similar to that of the patients in the pilot. Over two-thirds were employed and just under two-thirds completed the trial, about the same for both nalmefene and placebo.

Published in 1999, the study was similar to the pilot, but this time the two dose regimens – 20mg or 80mg daily – straddled the 40mg previously found effective, and were accompanied by fully-fledged cognitive-behavioural therapy over 12 weekly sessions. Return to heavy drinking was significantly and substantially less common among the nalmefene patients, regardless of dose, and this was also the case among the sub-sample of patients who had tried taking a drink. Three of the 80mg patients dropped out of treatment due to adverse effects, suggesting to the researchers that 20mg to 40mg was enough to gain the desired drink-suppressing impact while not unduly risking deterrent side effects.

Another US trial was funded, aided and overseen by Biotie, the company which sold the rights to nalmefene to Lundbeck, but most of the authors (including those leading the study) were prominent researchers with no acknowledged debt or connection to the company. Again, establishing an optimum dose was a prime objective. It seems the sole example of a trial not heavily influenced by nalmefene's manufacturers which came close to testing the same dose (though daily rather than 'as needed') with similar psychosocial support and similar patients as in the Lundbeck trials – and it found no significant impact relative to placebo.

Conducted at 13 US sites and published in 2004, the study had used ads and direct referral to recruit 277 patients who were randomly allocated for 12 weeks to placebo or one of three daily doses of nalmefene: 5mg, 20mg or 40mg. Unlike other trials, they had to have shown they could be abstinent for three days in a row during the period between being screened for eligibility for the study and starting treatment. Four sessions of therapy based on motivational interviewing accompanied the medication. In intensity, style and intention it seems to have been very similar to the psychosocial support offered patients in the Lundbeck trials and to the support the company expected to be provided alongside Selincro in normal practice in Britain.

At the start of the trial the patients were drinking on about 8 in every 10 days, on each of those days averaging about 118g alcohol or 15 UK units. Many were married or in relationships and/or employed – quite similar to the patients in the Lundbeck trials. The usual side effects such as nausea, insomnia and dizziness afflicted substantial minorities of the nalmefene patients, but on drinking, even at the highest dose there was nothing close to a significant impact relative to placebo even given the many measures taken, and craving for alcohol too was unaffected. These results were not due to failure to comply with treatment: over 90% of the pills were taken as intended.

Biotie funded – and in this case also played a large part in the study design and analysis of results – a further trial conducted at 15 sites in Finland, which prefigured the Lundbeck trials. Published in 2007, it seems the first to have tried nalmefene on an 'as needed' basis; patients were told to take a tablet preferably one to two hours before anticipated drinking. Lundbeck's 20mg dose was also settled on.

Recruited through ads for people experiencing difficulty controlling their heavy drinking, 403 participants were randomly allocated for 28 weeks to nalmefene or to a placebo, accompanied by the same low-intensity clinical support offered in Lundbeck's trials. Though heavy drinkers, exclusion criteria helped ensure participants were relatively stable; most were in live-in relationships and/or employed. On average they drank nearly every day and on each drinking day consumed about 115g alcohol or just over 14 UK units, over 9 in 10 were dependent, and 4 in 10 had previously been treated for their drinking.

By the end of the trial the drinking of just 233 or 59% of the patients could be re-assessed, but the effects noted below were apparent during the first four weeks, when nearly 90% of the patients were re-assessed. By the end a higher proportion were missing on nalmefene than placebo, partly due to adverse effects leading patients to withdraw. Based on the patients who were re-assessed, there had over the 28 weeks been significantly greater reductions in heavy and (especially) very heavy drinking and in overall consumption on nalmefene (down to 40g a day) than on placebo (down to 49g).

European authorisation

For the European market, the key decision on nalmefene was taken by the European Medicines Agency (EMA) when in 2013 it authorised the drug's marketing for the treatment of alcohol dependence under manufacturer Lundbeck's trade name, Selincro. The specific conditions to the drug's use recommended by the EMA (▸ panel) derived partly from how it had been evaluated in the two Lundbeck trials (1 2) on which authorisation was based, and especially on the tendentious analysis of high-risk drinkers from those trials. A further similar trial had extended the follow-up period to 52 weeks, and its results were cited in the product description associated with the authorisation.

Given the provenance, selectivity and shortcomings of the critical analyses, a decision nevertheless to allow Selincro to extend pharmacotherapy to less severely dependent drinkers was likely to be contested. It is important, however, to remember the prize held out to the European Medicines Agency by the drug's manufacturer: a chance to extend the benefits of treatment to a far greater proportion of dependent drinkers, the vast majority of whom would not consider onerous treatment regimens predicated on total abstinence.

European Medicines Agency authorisation

Selincro is used to help reduce alcohol consumption in adults with alcohol dependence who consume more than 60g [7.5 UK units] of alcohol per day for men or more than 40g [5 UK units] per day for women.

It should only be used ... in people who do not have physical withdrawal symptoms and who do not require immediate detoxification.

Selincro should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.

Selincro should be initiated only in patients who continue to have a high drinking-risk level two weeks after initial assessment.

Authorisation was granted, but the process was not straightforward, resulting in the unusually constrained recommendations for who the drug should be prescribed to. Primary, planned in advance results from what the EMA called the two "pivotal" trials (1 2) were seen as unconvincing by the agency's committee: "differences in treatment effect between nalmefene and placebo were considered ... small, not consistently statistically significant across co-primary endpoints, and with a degree of uncertainty with regards to clinical relevance in the total population."

Given this hesitation, Lundbeck supplied an analysis (later published) focused on the "high risk" drinkers (for men averaging at least 60g a day, women 40g) who stayed that way during the week or two between screening for eligibility and the start of treatment, excluding the medium risk drinkers and the heavier drinkers who remitted even before treatment started. It was, said the EMA's report, "proposed" by Lundbeck "in order to define a population where the benefit of Selincro would be greatest", a formulation which could be interpreted as an attempt to find a way of

the benefit of Selincro would be greatest", a formulation which could be interpreted as an attempt to find a way of selecting a sub-sample advantageous to Selincro. Despite being mounted late in the day when the data was already known – and therefore an unreliable indicator of effectiveness – the high-risk drinkers were thought the ones most likely to be prescribed Selincro in routine practice, enhancing clinically relevance. As expected, the consumption-curbing effects of nalmefene were more pronounced in these heavier drinkers who had more scope to cut down at the time treatment started, but still at first the European Medicines Agency's committee thought the magnitude of beneficial effects remained "inconsistent ... and that its clinical relevance had not been fully elucidated." They sought further advice, but in the end formulated their conclusions based largely on this sub-sample, limiting their recommended use of the product to just this type of drinker.

It meant that it was substantially on the shoulders of 413 patients – the heavy drinkers who stayed that way between screening for eligibility and the start of treatment and supplied final follow-up data – that European authorisation of Selincro rested. They had been recruited at 96 European sites over 15 or 17 months, about one every four months at each site. It is hard to deny the probability that they were a highly selected and atypical set of heavy drinkers. They will have been more typical of those who enter a trial and do not substantially reduce drinking before treatment starts, but these are not necessarily the same patients who if they were seeking treatment in the normal way would also sustain heavy drinking over the first two weeks after contacting a treatment provider – one of the criteria ported from the trials into the product's authorisation.

Crucially, the committee confined its consideration of naltrexone – nalmefene's cheaper parent drug – to whether nalmefene's "pharmacokinetic, pharmacodynamic and toxicological properties" – limited aspects of its technical pharmacological profile – meant it could be considered a derivative of naltrexone. They decided not, clearing the way for authorisation. There was no consideration of whether *clinically* – in their intended treatment roles and effects – the two medications might be equivalent.

Six of the committee dissented from the majority verdict. Despite Lundbeck's estimates of the lives which could be saved by nalmefene-generated drinking reductions, in the trials themselves the dissenters saw "no direct evidence of harm reduction ... The treatment effect observed in the pivotal studies translates into approximately 2 fewer [heavy drinking days] per month and 1–2 drinks fewer per day for patients treated with nalmefene compared to those who received placebo ... The majority of participants continued to have significant levels of [heavy drinking days] and daily levels of consumption of alcohol. The clinical significance of this modest reduction in alcohol consumption has not been demonstrated in these studies."

Criticism of the EMA's decision in the pages of the *British Medical Journal* (1 2) was rebutted by the authors of the studies on which authorisation relied, and some complaints were indeed knocked down. Left standing however were the observations that the decisive sub-sample analysis relied on a minority of originally randomised participants, that such analyses are considered unreliable evidence of effectiveness, and that naltrexone might be a cheaper alternative.

Could naltrexone play Selincro's role more cheaply?

The European Medicines Agency's decision meant Lundbeck could market Selincro, but did not mean health authorities had to buy it and make it available to patients. First they would have to be persuaded it was at least as safe and cost-effective as the alternatives.

A key comparison was with the cheaper parent drug, naltrexone. Finding clear blue water between these medications was important to Lundbeck. If medical regulators and national guidance placed nalmefene in the same clinical ball park as naltrexone, the effect would be to expose Selincro to competition from a cheaper generic (ie, non-patented) product – profit-hitting competition which Selincro and other new products were meant to counteract. In this situation there would be little reason for publicly funded services to spend more on nalmefene in the form of Selincro. Though not specifically authorised for this purpose, in fact, naltrexone has successfully been trialled with the same kinds of patients for the same treatment objectives and used in the same 'as-needed' way as Selincro, and might well be able to fulfil the role earmarked for the new product just as well and more cheaply. No one can know for sure until head-to-head trials are run, but current evidence leans further towards equivalence than difference between the medications.

Clinically insignificant differences

Similarities between nalmefene and its more familiar parent compound naltrexone are such that it would be surprising if there were appreciable differences in their impacts on drinking. Chemically, nalmefene is derived from and closely related to naltrexone. Pharmacologically, both reverse the effects of opiate-type drugs – they are 'opioid antagonists'. Clinically, both have been trialled in the treatment of alcohol dependence, on the basis that the rewards drinkers experience from drinking are partially mediated by the opiate receptors in the brain which opioid antagonists adhere to and block. There are differences in how strongly the compounds adhere to different kinds of opiate receptors and in how they are metabolised, but these have been described as causing "minimal if any differences in efficacy for reducing heavy drinking". Their side-effect profiles are also similar, except that the risk of liver toxicity with naltrexone at doses well above those used in the treatment of alcohol dependence seems absent for nalmefene.

The suspected mechanism via which naltrexone works is that patients drinking under its influence find the expected pleasurable effects muted, and as a result the impetus to drink becomes 'extinguished'. If this was the case, it made sense to the author advancing this mechanism for naltrexone to be taken as needed in anticipation of drinking, a strategy which trials proved effective. If the patient did drink after taking the pill, consumption would be depressed and the experience would further extinguish the impetus to drink. The suspected mechanism, expected effects and the 'as needed' strategy are similar to those the manufacturer suggests for nalmefene .

Nalmefene is intended to be prescribed without pre-treatment detoxification, and in naltrexone trials too, prior detoxification has been the exception. However, rather than nalmefene's reduced-drinking objective, most naltrexone trials have stipulated abstinence as the goal, and the UK's medicines regulator defines the drug's role in alcohol dependence as to "support abstinence". But they go on to acknowledge that naltrexone's "prominent effect seems to be a reduction of the risk of a full relapse with uncontrolled binge-drinking after having consumed a limited amount of alcohol" – the role intended for Selincro. Notwithstanding abstinence goals, in trials naltrexone's main effect (1 2 3) has been to 'normalise' drinking towards fewer heavy drinking days and lower consumption on each occasion, rather than stopping drinking altogether. Reduced drinking rather than a delay in return to drinking was also the main effect in the major British trial. That this is how the drug works has been acknowledged by the UK's health technology assessor. Compared to other major medications for alcohol dependence, in practice naltrexone is thought more suitable for people not aiming for or who find it hard to stop drinking altogether, and with a strong desire to drink in order to achieve what they experience as a pleasurable state of intoxication rather than to avoid withdrawal symptoms – similar to Selincro.

Naltrexone may be most effective in more heavily drinking alcohol-dependent patients, but so too is nalmefene, and naltrexone seems to remain effective among patients averaging around 106g per day, the level in the analysis on which

naltrexone seems to remain effective among patients averaging around 106g per day, the level in the analysis on which nalmefene's authorisation was substantially based.

Commercially significant differences

The differences between the medications are more to do with regulation, guidance and commercial considerations than clinical properties. One such difference is that UK prescribing guidance specifies naltrexone be initiated under specialist supervision for "formerly" alcohol-dependent patients, recommendations which would constrict its market to drinkers prepared to and who can attend specialist clinics, and who start naltrexone having already ended dependent drinking. No such restrictions limit nalmefene's market, and it is hard to see how they remain justified for naltrexone.

Another difference between the medications is in price. Under patent protection (1 2) for these purposes and with Lundbeck ceded global rights to the compound, nalmefene in the form of the branded product Selincro has an NHS indicative price of nearly £85 for 28 tablets, while from some manufacturers the corresponding price for naltrexone dips below £20.

It can be countered that nalmefene would last longer because it need not be taken every day. The counter-counter is that to the degree that it is not taken, it will be less effective at reducing drinking, and that naltrexone too (▸ below) can be taken 'as needed', with no apparent detriment to effectiveness.

Naltrexone has also successfully been trialled in Selincro's market – in primary care circumstances, and taken as needed by the kind of mildly and moderately dependent drinkers at whom Selincro is targeted, making it unclear what nalmefene brings to the table which was not already there at a lower price. On clinical rather than commercial grounds, there seems no reason why authorisation could not have been sought for a naltrexone product with the same remit as Selincro. That this did not happen may have been due to no pharmaceutical company having sought such a decision, presumably partly because the returns on the generic drug naltrexone would be lower.

Naltrexone trials suggest nalmefene-type impacts

Naltrexone trials have shared many of the features of Lundbeck's nalmefene trials, testing the drug among similar patients who used it 'as needed' – but without in the outcome analysis giving naltrexone the advantage given nalmefene of selecting only the heavier, high-risk and above drinkers who stayed that way during the week or two between joining the trial and starting treatment, so had most scope to cut back. Nevertheless, naltrexone's effects seemed to compare well with nalmefene.

Conducted in Finland in Northern Europe, where Lundbeck also sampled, one trial recruited 121 drinkers, nearly three-quarters of whom were men. Like the men among the high-risk drinkers with whom nalmefene was found effective, to join the study they had to be averaging at least 60g alcohol a day. Also as in Lundbeck's nalmefene trials, participants were mainly employed and living with partners and families, had usually never before been treated for their drinking, and had not been detoxified before starting treatment. Other similarities were the criteria for joining the study, which resulted in a relatively stable set of patients, and a modest psychosocial programme – four group sessions either cognitive-behavioural or supportive in nature.

After 12 weeks of daily dosing, participants were told for the next 20 weeks to take a pill only when they felt at risk of drinking. As in Lundbeck's trials, rather than abstinence, the main yardstick of success was avoiding a return to heavy drinking of the kind which qualified the patients for the trial. Patients had been randomly allocated to medication versus placebo and to the two types of psychosocial support, so it was valid to compare the effects of naltrexone within each support regimen.

Of most interest were the cognitive-behavioural patients because – as in the nalmefene trials – the therapy's focus was not on abstinence, but on preventing high-risk drinking. Offered naltrexone, around 27% of these patients managed never to slip back to heavy drinking, but on placebo, virtually none – just 3%. The difference was highly statistically significant, and a similar gap was seen in the proportions of patients reporting multiple relapses. The closest reported comparator among the Lundbeck trials' high-risk drinkers was a small extra reduction of 3.2 days of heavy drinking in the last 28-day period on medication.

By the last eight of the 32 weeks on naltrexone, total consumption too was significantly less, averaging 231g a week compared to 354g on placebo, an extra reduction equating to nearly 18g a day. In the Lundbeck trials, the corresponding extra reduction among high-risk drinkers was 14g a day.

More distant literally and in drinking culture from the nalmefene trials was a US trial of naltrexone among patients recruited through ads or by referral. As in the Lundbeck trials, they could choose to aim to reduce drinking (in this case to within safe levels) rather than to abstain. They were also at worst mildly dependent, but had to have been averaging at least 48g a day for men and 36g for women, and very few had previously been in treatment – patients in Selincro's ball park. Low-intensity, fortnightly brief coping-skills therapy accompanied placebo or naltrexone, and in randomly allocated patients the pills were to be taken for eight weeks either every day or 'as needed'. As with nalmefene, 'as needed' patients were encouraged to take a tablet one to two hours before an anticipated high-risk drinking situation.

Across all the patients, naltrexone led to a 19% extra reduction in the proportion of heavy-drinking days. Until in the final three weeks of the eight they began to run out of tablets, generally the as-needed naltrexone patients best avoided heavy drinking. By (rough) comparison, among high-risk drinkers in the Lundbeck trials, at the end of 24 weeks the extra reduction in heavy-drinking days on nalmefene was 3.2 days or around 14%, a figure which seemed about the same at the eight-week follow-up. Across all the patients in the two nalmefene trials which underpinned European authorisation, the extra reduction in heavy drinking days at the end of 24 weeks was respectively about 12% and 9%.

Returning to Finland, another trial compared daily followed by as-needed naltrexone not with a placebo, but with disulfiram or acamprosate prescribed according to the same regimen. All the medications were accompanied by brief cognitive-behavioural therapy. Reduced drinking was the aim with acamprosate and naltrexone, but with disulfiram – which produces aversive physical reactions after drinking – abstinence was the objective. Patients did not have to have been detoxified and were required not to be suffering withdrawal symptoms.

Both during daily treatment (when administration of the drugs was supervised by one of the patient's associates) and when the drugs were taken as needed, alcohol consumption was much lower on disulfiram; in the as-needed period, it was under half that with naltrexone. The results show that among patients prepared to countenance disulfiram, it too can be taken as-needed, and be much more effective than naltrexone and, by extension, probably more effective than nalmefene. Due to adverse reactions after drinking, disulfiram patients must be well informed and carefully monitored, but given these circumstances, it seems well suited to as-needed administration, giving patients a compelling reason

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Other trials have tested daily rather than as-needed naltrexone, but have sampled moderately dependent drinkers or those whose condition is not complicated by multiple and severe problems and who were still drinking when they started treatment – the kinds of patients likely to be treated in primary care. In these patients daily naltrexone has been found to significantly reduce drinking, again placing it in same clinical ball park as Selincro.

In particular, naltrexone's effect has been to raise the anti-drinking impact of the type of support provided in primary care to the level achieved by specialist psychological therapies (1 2). A review which investigated this issue found that relative to placebo, naltrexone augmented the effects of typical, less structured forms of psychosocial support such as counselling, but not structured, manualised programmes, which were generally cognitive-behavioural in nature. The implications are that naltrexone can be a valuable supplement to clinical support for dependent drinkers, especially when specialist therapies such as cognitive-behavioural therapy are refused or unavailable – a Selincro-like role.

Questionable 'first indication that nalmefene is superior'

Though there are no known head-to-head treatment trials, an analysis seemingly sponsored by nalmefene's distributor Lundbeck has compared outcomes from trials which tested one of the two drugs against a placebo among patients with "high alcohol consumption". The three authors were a researcher whose work had been financially supported by Lundbeck, an employee, and an analyst commissioned by the company.

Results for nalmefene were amalgamated from trials sponsored by its manufacturers in which it was to be taken 'as needed', and for naltrexone from trials in which it was to be taken routinely every day. Of four comparisons of drinking reductions relative to placebo, one was significantly greater for nalmefene than naltrexone, and the remainder also favoured nalmefene without achieving statistical significance. In nalmefene trials measures of drinking consistently fell to a significant degree from before treatment to 12–24 weeks into treatment, but the same yardsticks were consistently non-significant for naltrexone. The incidence of adverse effects did not significantly differ.

It was enough for the authors to say their results "may give the first indication that nalmefene is superior to naltrexone in the treatment of alcohol dependence, at least on the basis of a harm reduction, 'treatment as needed' approach." But the comparisons which generated this optimism were largely invalid; it seems that only in the three Lundbeck-sponsored nalmefene trials (1 and 2; 3) did the analysts select only participants who had started the trials at high risk or above drinking levels (for men averaging at least 60g a day, women 40g) and remained at that level one or two weeks later when they started treatment, discarding over half the patients who contributed to the full-sample outcomes analyses.

In the original studies this sub-sampling was expected to give nalmefene greater scope to reduce drinking by eliminating patients who had already cut down before treatment started – an advantage gifted nalmefene in the three largest of the four trials included in the analysis, but not replicated for naltrexone. In naltrexone trials, whole samples were included whether or not they met the Lundbeck trials' high-risk drinking criterion, and whether or not they had cut down on signing up for the trials but before treatment had started. Only a reader who knew or consulted the source studies cited in the review would realise the results were subject to this serious source of bias.

Access to unpublished data from Lundbeck might have allowed the analysts to select all the high-risk drinkers whether or not they cut down before treatment, bringing the samples closer to those in the naltrexone trials, and perhaps also to bring the outcomes compared across the trials into closer alignment, but neither seems to have been done. For three of the four naltrexone trials, they used measures quite different from the 'heavy drinking days' measure used in the nalmefene trials. In these three trials, the selected measure replaced or diluted heavy-drinking days with days when patients drank at all. Since naltrexone has a greater impact on heavy drinking than drinking as such, the effect was probably to disadvantage the drug relative to nalmefene. In two of the naltrexone trials (1 2) a measure closer to heavy drinking days was available.

Naltrexone and nalmefene go head to head

Seemingly the only published study to have directly compared naltrexone and nalmefene was not a treatment trial, but a US laboratory study published in 2003 which had recruited dependent and social drinkers not seeking treatment, who had ostensibly joined the study to test the effects of the drugs.

Randomly allocated, for five days they took one of the medications (increasing to 40mg a day of nalmefene and 50mg naltrexone) or a placebo, and then spent the day in a simulated bar in a laboratory where they were given an alcoholic drink and then could either consume up to four more drinks, or instead earn money for not drinking. In the five-day lead in period, on either of the medications the dependent drinkers in the sample drank less than on placebo to roughly the same degree. Among the low consumption social drinkers, there was no impact. Findings were similar in the laboratory, where the dependent drinkers more often abstained and drank less if they had taken either of the two active medications, but with no significant difference between the two. Nalmefene's side effects more often led participants to leave the study than those of naltrexone.

This study was disregarded in the Lundbeck-influenced review described above on the grounds that "The dose of nalmefene ... did not correspond with the approved dose for nalmefene in Europe. Thus, these data cannot be used to compare nalmefene with naltrexone." What the reviewers did not say was that the nalmefene dose was actually double the approved dose, and that there was no reason to believe it would be less effective curbing drinking than a lower dose.

UK follows the European decision

Just because Lundbeck could market Selincro in the UK and elsewhere in Europe did not mean health authorities in those countries had to buy it and make it available to patients. First they would have to be persuaded it would be beneficial in their own contexts and that it was safe and value for money, a decision involving comparison with established alternative approaches, not just with a psychosocial programme whose main aim was to get patients to use inactive placebo pills.

For the UK the breakthrough came in 2013 when Scotland recommended Selincro be made available for the treatment of alcohol dependence, a recommendation whose form duplicated the European marketing authorisation. The recommendation was not free of reservations. In making its decision, the Scottish Medicines Consortium expressed concerns about the solidity of the research which led to Selincro's authorisation. The "main evidence", they said, came from "post hoc analyses of a sub-sample of heavy drinkers in the first two Lundbeck trials which "were not powered for these subgroup analyses and the effect of initial randomisation may have been lost." In other words, the sub-samples were too small to be sure of the results, and selecting them might have tilted the level playing field intended to be

assured by random allocation of the full samples

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Nevertheless, the consortium felt the company's cost-effectiveness analysis of nalmefene plus psychosocial support versus psychosocial support alone was robust in its findings that the drug would inexpensively improve and prolong life. Interestingly, this modelling assumed that Selincro would not displace any other medication, confirming that it was expected to carve out an entirely new pharmaceutical market. Since "No other medicines are specifically licensed for reducing alcohol consumption" as opposed to sustaining abstinence, the assessors found no need to demand the new product prove itself against medications such as naltrexone. In all these considerations, the consortium prefigured the key decision for the much greater market in England and Wales later taken by the National Institute for Health and Care Excellence (NICE).

Wales followed suit, recommending nalmefene for NHS use in 2014. But the assessors complained that "The company did not include a pharmacological comparator in the economic analysis", noting that NICE had recommended that acamprosate or naltrexone be considered for mildly dependent drinkers who have not responded to psychological intervention, and that the medications had been used in this way in Wales, making them rivals to Selincro despite not being licensed for the same purposes.

NICE recommends Selincro

Later in 2014 the Welsh decision was superseded by that of Britain's National Institute for Health and Care Excellence (NICE), one which opened up the entire UK market.

In 2011 NICE had already recommended acamprosate or naltrexone for a population substantially overlapping that targeted by Selincro – mildly or moderately dependent drinkers, and especially those who have not responded to the psychological interventions it recommended, among which were cognitive-behavioural therapies, behavioural therapies, or those based on engaging the patient's social network and/or their partners in the treatment effort. Neither acamprosate nor naltrexone were to be offered in isolation, but in combination with these kinds of therapies.

The issue was whether to add nalmefene to this medication suite, mandating that it be made available by NHS-funded services. To jump to the end, the decision was that these services must make nalmefene available for the uses and for the patients stipulated by the European Medicines Agency. Importantly, the decision followed Europe in mandating continuous psychosocial support without requiring it be of the intensity and type NICE had recommended accompany the other medications.

In advance of its appraisal, NICE had 'scoped' what it would be important to know. They stipulated two comparators for nalmefene in conjunction with psychological therapies: versus naltrexone plus the therapies it had previously recommended; or versus these therapies alone; NICE wanted to know not just whether nalmefene was effective, but whether it was more or less effective than approaches they had already recommended.

In the event, neither of the comparisons were in Lundbeck's submission to NICE, yet there had been at least two studies in which nalmefene plus psychological therapies had been compared with these alone plus placebo. In one of these the therapy matched NICE's recommendations, yet still nalmefene substantially augmented reductions in heavy drinking. In another in which the psychosocial support was more basic, nalmefene had not improved on a placebo. According to the company, this more basic programme based on motivational interviewing was the one closest to the support recommended to accompany nalmefene.

Cost-effectiveness relative to psychosocial care

Lundbeck's cost-effectiveness submission to NICE confined itself to its own trials. It meant that instead of the fully-fledged therapies envisaged by NICE, the psychosocial care supplementing both nalmefene and placebo was the more basic package organised for the nalmefene trials – a low-intensity but well-structured clinical programme focused on compliance with treatment. Lundbeck's argument was that this resembled how most such patients were treated in Britain.

From their three trials (1 and 2; 3) the company selected only the high or very high risk drinkers (men averaging at least 60g a day, women 40g) who remained in that range one or two weeks later when they started treatment, discarding over half the patients who contributed to the overall outcomes analyses. The justification was that this was the "licensed" population specified in the European marketing authorisation – which it was, but only because Lundbeck and the researchers it recruited had decided to split the samples using this criterion. Having made this decision, which left nalmefene performing more convincingly than in the full samples, this advantage fed through to authorisation and determined the form that took, and then authorisation was used to justify its perpetuation in the cost-effectiveness analysis, which in consequence retained the vulnerability to bias introduced by the initial decision.

With the benefit of (as critics wryly termed it) this "refinement" of the samples, nalmefene emerged as costing less overall, not just in terms of the treatment itself, but in this plus health, social and crime costs imposed by the patients and the costs of further treatment in case of relapse. Despite costing less overall, nalmefene was estimated to gain for the patients longer and better lives, calculations which made it a relative bargain. According to the manufacturer's figures, it would take a very large 70% decrement in nalmefene's effectiveness relative to the comparator for it no longer to score as a cost-effective use of resources.

Two similar analyses published after NICE made its draft appraisal of nalmefene seemed to have built on the company's submission. Of the nine authors of a report on the first analysis, the lead author and two others were at the time Lundbeck employees, another three had been contracted by Lundbeck, and the remaining three had received an honorarium from the company for participating in the study. They calculated that over a five-year period Selincro patients would gain one year of life adjusted for quality at a cost to the health service of £5204, comfortably within the £20,000 to £30,000 range above which treatments are conventionally deemed too expensive. Among the benefits contributing to this calculation were the avoidance of 7179 alcohol-attributable diseases or injuries and 309 deaths per 100,000 patients. Later this analysis was extended by taking account of patients whose drinking has become or remained so severe that they would need medically assisted detoxification followed by further treatment. On this basis, not only would nalmefene patients end up costing the health service less than those offered psychosocial care alone, but they would also benefit from extended/improved lives.

All these calculations were based on a comparison with psychosocial support whose main focus in the placebo arms of the trials was in effect to get patients to use inactive pills – not a recommended or real-world alternative to nalmefene. Expert reviewers drafted in by NICE to scrutinise Lundbeck's arguments pointed out that the intended comparison was with the fully-fledged, standalone psychosocial therapies NICE had previously recommended. To get closer to this intention, they compared these therapies against nalmefene plus the more basic clinical support provided in the Lundbeck trials. With no head-to-head trials, they used evidence from trials which had compared the psychosocial therapies to other approaches or no treatment – very much a second-best strategy, as patients and situations will

therapies to other approaches or no treatment – very much a second-best strategy, as patients and situations will have differed in these trials versus the nalmefene trials. Despite the different comparator, the reviewers reached a similar conclusion to the company: only if nalmefene's extra advantage relative to placebo was greatly eroded by the psychosocial therapies – by 63% – would the medication no longer seem cost-effective. Whether this degree of whittling down would happen, they were unable to say.

However, this analysis retained and then amplified the fundamental weakness in the company's analysis – that it was based on an after-the-event sub-sample of under half the full samples, selected to give nalmefene a better chance to prove effective, but in the process making the results vulnerable to bias. As in a comparison with naltrexone, this weakness was amplified because no such advantage could be given to the psychosocial therapies against which nalmefene was compared.

The feasibility of replicating in routine practice something like the psychosocial support offered in the Lundbeck trials was another major issue in NICE's considerations and consultation responses. Lundbeck's response to NICE's draft guidance had stressed that the "continuous" support mandated in the marketing authorisation should be seen as "very similar to what is commonly used in routine clinical practice for the management of other long-term or chronic conditions" – not a specialist therapy, but "similar in level of intensity and duration to a brief intervention or extended brief intervention". Still there was concern on the NICE committee that many GPs – the envisaged locus for most of the prescribing of nalmefene – would feel they had neither the skills or the time to offer such support. One consultee identified as an NHS professional went further, foreseeing that nalmefene would displace rather than supplement psychosocial support: "in primary care, a psychosocial element to treatment will be offered rarely ... The potential for widespread implementation of psychosocial treatments to reduce alcohol related harm is huge, but it isn't going to happen because of nalmefene."

Cost-effectiveness relative to naltrexone

The other comparison NICE thought they would need before recommending nalmefene was versus naltrexone, in respect of which direct evidence was entirely absent. Lundbeck could still have indirectly compared the two medications by comparing how much better than placebo nalmefene was against the same metric for naltrexone, but this they declined, arguing that needed data was lacking from the naltrexone trials, and that these were in any event so different from the nalmefene trials that a comparison would have been invalid. "Should the manufacturer have undertaken an indirect comparison, albeit an imperfect one?" was the question posed to the NICE committee before it met, the observation being made that Lundbeck could have asked study authors for the missing data.

After having declared an attempt to compare nalmefene and naltrexone invalid due to differences in the trials, later Lundbeck sponsored (and a Lundbeck employee co-authored) just such a comparison, but too late for NICE to take it on board. The resulting lack of evidence meant NICE's assessors could not include this key comparison with a much cheaper but possibly equivalent medication in their consideration of whether the new product represented value for money. In fact, there is evidence suggesting that taken as needed and among the same types of patients on whom Lundbeck had tested nalmefene, naltrexone would have led to similar reductions in drinking, but it seems this was never systematically placed before NICE's committee.

Some of those consulted on the draft guidance remained unconvinced by NICE's acceptance of Lundbeck's arguments that a comparison with naltrexone was not feasible, and that in any event the two drugs were licensed for different purposes – nalmefene to reduce drinking in non-physically dependent drinkers, naltrexone to sustain abstinence among drinkers who may have needed prior detoxification. In practice, said the National Substance Misuse Non-Medical Prescribers Forum, the two medications are equivalent: both could be taken as needed, and taken that way, neither would appreciably risk liver damage, yet "naltrexone which can be prescribed as a generic pharmaceutical product in the United Kingdom has significant savings over nalmefene." Complaining that the draft guidance lacked a cost-effectiveness comparison with naltrexone, the substance use charity Turning Point "disagree[d] with the statement that naltrexone would be used in practice to treat a different patient group than those included in the nalmefene trials, with abstinence as the treatment goal." Instead, they argued, treatment providers may decide to use the cheaper naltrexone despite its not being specifically licensed for the same purposes as nalmefene. They welcomed the new option, but queried its cost-effectiveness relative to naltrexone.

NICE reaches its decision

Experts who scrutinised Lundbeck's submission for NICE saw gaps in comparisons with naltrexone and with psychological therapies as the main limitations of the company's attempt to show their product would be a cost-effective addition to the NHS's alcohol treatment armoury.

Unable to pronounce on these comparisons due to lack of evidence, the experts nevertheless felt that reserving nalmefene for patients who did not benefit from psychological therapies – as NICE had recommended for other medications in cases of mild dependence – would be more cost-effective than offering the medication to everyone still drinking heavily two weeks after contacting a treatment provider. Had their view been accepted, it would have relegated nalmefene to a second-order treatment tried if at all only after several months, a process which would tend to limit its market to quite severely dependent drinkers unresponsive to 'talking therapies'. Such patients might also be thought suitable for naltrexone or acamprosate, and the therapies concerned are generally only available in specialist clinics. The result was likely to have been a substantial hit to Lundbeck's potential market.

With this advice before them, the NICE committee responsible for making the decision seemed more forgiving than the reviewers commissioned to examine the company's case. Advised by clinical experts, the committee rewrote the remit they had been given by NICE, entirely ruling naltrexone out of the equation and accepting a drastic dilution of the psychosocial support comparator. The two comparisons which in advance NICE had seen as required to appraise nalmefene were rejected as inappropriate.

Naltrexone dismissed

Naltrexone was completely dismissed on the grounds that – according to the clinical experts – it was not routinely used to reduce rather than eliminate drinking. In the words of NICE's guidance report, "The Committee had heard from the clinical experts that naltrexone plus psychosocial intervention was not part of established practice for the reduction of alcohol consumption, and it agreed that naltrexone plus psychosocial intervention could not be considered an appropriate comparator. The Committee concluded that it would not consider further the comparison of nalmefene plus psychosocial support compared with naltrexone plus psychosocial intervention in its decision-making."

In this the committee seemed to accept that established practice could not be changed for naltrexone, while at the same time recommending it be changed by introducing nalmefene. Arguments that if nalmefene can and should be used

to reduce drinking, so too could naltrexone, and that it actually had been used in just this way, held no sway, and the

to reduce drinking, so too could naltrexone, and that it actually had been used in just this way, held no sway, and the studies which showed naltrexone worked with nalmefene-type patients and objectives seemed not to have been considered.

Psychosocial support diluted

In respect of psychosocial support, current practice too seemed accepted as a fixture, despite falling short of NICE's recommendations. The committee accepted that in practice the kind of psychosocial support provided in the Lundbeck trials would be the alternative to nalmefene. Based on a sub-sample analysis of the trials, adding nalmefene to this support seemed to have cost-effectively improved outcomes, so it followed that nalmefene should be recommended. Contrary views were that the sub-sample analysis was vulnerable to bias and not suitable for proving effectiveness or, by extension, cost-effectiveness, and that the psychosocial support programme offered in same trials was neither desirable nor practical.

As with naltrexone, "clinical experts" were influential: "The Committee heard from the clinical experts that the current services available in England have difficulty providing the level of psychosocial interventions recommended in the NICE guideline on alcohol-use disorders." The same experts advised that the support made available in Lundbeck's trials, though "not used in its entirety in clinical practice, most of the components within it are currently provided in the form of brief or extended brief interventions and could be administered by healthcare professionals."

There is indeed overlap in style and content between the BRENDA programme used in Lundbeck's trials and brief interventions, but also a fundamental difference. BRENDA's main aim is to motivate patients to take their medication as prescribed, while the brief interventions GPs are familiar with are aimed at people not in treatment and not even seeking help for their drinking. Most evaluated brief interventions avoid advising the client on how they should deal with their drinking, trying in motivational-interviewing style to elicit these commitments and plans from their own mouths, while in BRENDA direct advice is a major component and consists of "discussion with the patient about how a particular intervention or medication would help him or her".

In their comments, NICE's clinical experts touched on another way BRENDA differed from clinical practice: it was both more structured and more extensive than would be usual. According to Lundbeck's submission to NICE, as implemented in their trials the programme was delivered by specially trained staff some of whom were not those routinely available at the site but investigators, and some of whom were not doctors or nurses but psychologists. Given the sites, it seems likely that few if any were generic primary care staff. Six sessions were delivered during the first 24 weeks of each of the three Lundbeck trials, described by the company as each lasting 15 to 30 minutes, except for the first which lasted 30 to 40 minutes. Over the 24 weeks that would total to a time commitment of from nearly two to over three hours. The typical GP consultation lasts 10 minutes, very few last half an hour, appointments on average every four weeks would be unusual, as would a manual and special training. (Complicating this issue is that one of the lead researchers in the trials has said the sessions lasted just 10–15 minutes.)

At one point Lundbeck's submission likened trial support to "planned" brief interventions – effectively brief treatment, interventions much lower down the intensity scale than NICE had recommended even for less severe alcohol dependence. In this context it is important to remember that the target population for nalmefene became not just anyone to any degree dependent on alcohol, but people averaging at least 60g a day for men and 40g for women with no upper limit, and who did not reduce risk in response to treatment entry. To accept brief interventions rather than fully-fledged therapies for these patients would be a bold step to take, contravening previous guidance.

Nevertheless, in its final report the committee accepted Lundbeck's case that the psychosocial support programme in their trials "was relevant to clinical practice in England", and that "psychosocial intervention in the form of brief or extended brief intervention is a valid comparator for nalmefene plus psychosocial support and the most appropriate comparator for this appraisal." The decision ruled out comparison with the psychological therapies NICE had previously endorsed for alcohol dependence, though these too might have been found (1 2) to shine as much as nalmefene in comparison to more basic clinical support.

NICE recommendation criticised

A systematic assessment of the two pivotal trials (1 2) led the respected *Drug and Therapeutics Bulletin* to come out decisively against nalmefene, questioning the basis for its European authorisation and NICE recommendations for Britain: "Based on the limitations of the evidence, the relatively modest reductions in drinking compared with placebo, lack of evidence on health-related outcomes and concerns over the generalisability of the data, we cannot recommend the use of nalmefene." Among the issues they identified were that even taken every day, naltrexone would cost less than half as much, that primary care would struggle to provide even the modest level of psychosocial support offered the patients in Lundbeck's trials, that the trials' participants were possibly unrepresentative of the intended patients, and that the small reductions in drinking were of unknown clinical significance; whether they would translate into better health was uncertain.

NICE's decision was the main target of a critique of the evidence for nalmefene from authors based in England and Scotland, fronted by pharmacist and lecturer in alcohol studies, Niamh Fitzgerald of the University of Stirling. They searched for and found six nalmefene trials including the three funded by Lundbeck on which European authorisation and NICE's decision were largely based. Each of the three trials was, they said, weakened by high-drop-out, and by decisions to add or refine the primary yardsticks of success after the trial had been completed, a procedure which means it is possible for researchers to alter criteria for success to fit the data – effectively, to move the goalposts. Most serious was in the one-year trial the decision late in the day to introduce drinking reductions at the 24-week follow-up as a primary yardstick when at first drinking was mentioned was only a secondary yardstick, and then as assessed at the 52-week follow-up – though this was not likely to have been done to produce significant results, because the opposite happened.

Just as serious and for similar reasons was the shifting of the goalposts in terms of the set of patients among whom nalmefene was assessed. As already noted, the focus was shifted from the total sample of patients in the first two Lundbeck trials to exclude medium risk drinkers altogether, and then include only those high-risk drinkers who did not respond to joining the trial by de-escalating their drinking to at least medium risk levels, an after-the-event "refinement' of the sample which "should not be regarded as anything other than hypothesis-generating". It was, of course, regarded as far more than that – as substantially the basis for allowing the company to market Selincro in Europe and to mandate Britain's National Health Service to make it available to patients.

The critics also highlighted that some ways of analysing the data found no significant benefits on some of the measures, including the method adopted by the featured review of assuming patients not followed up had relapsed to or continued their pre-trial drinking. Criticised too was that NICE had made its decision without knowing whether nalmefene as used in the Lundbeck trials was an advance on currently recommended treatments, including naltrexone

nalmefene as used in the Lundbeck trials was an advance on currently recommended treatments, including naltrexone and psychological therapies. Then there was the issue of whether, as Lundbeck's cost–effectiveness calculations assumed, primary care practices would embrace and be able to deliver nalmefene as envisaged in guidance and tested in the trials, with a structured psychosocial support programme more demanding than other interventions GPs have failed to deliver. The critics pointed out that none of the trials shed light on this issue, because none had been conducted at free-to-access primary care services. Finally, the company marketing the medication had been deeply involved in all the trials on which regulatory decisions had relied, yet such decisions "require evidence unbiased by vested interests".

Concern that a drug targeted at less severely dependent patients would be a step "backwards" was voiced by the lead author of the critique. Though a pharmacist, she foresaw that "the drug will lead to medicalisation of a level of alcohol problem that would not normally be medicated ... in such a way that more people are led to believe they have medical conditions which can, or even ought, to be treated with medication." Particularly under threat were the brief interventions which Lundbeck saw as close cousins to the psychosocial support provided in its nalmefene trials. Given the well-known reluctance of many GPs to do structured brief interventions, the risk was that Selincro would not supplement but displace these, using up health resources which could have been used to implement more effective psychosocial interventions such as multiple-session brief interventions. Worse still, the concern was that many people who would have remitted from their heavy drinking on their own would find themselves being medicated instead.

Lundbeck has provided resources which might inadvertently make it easier for Selincro to do what the critic feared and displace face-to-face brief interventions and brief treatment. Basic as it was, the support programme in the Lundbeck trials exceeded in time and structure the typical primary care consultation, and "continuous" might be taken to mean frequent, long-term contact. Lightening the load for primary care services, Lundbeck has created a web-based therapy programme to provide "comprehensive ongoing support for the patients in between consultations", and "supported the development of a psychosocial support booklet provided as a service to medicine, for use by healthcare professionals that are less experienced in delivering structured psychosocial support to a patient with mild alcohol dependence." By offering these, GPs unable or unwilling to provide what for primary care is a relatively intensive, structured, face-to-face support programmes, would still be able to see themselves as meeting the psychosocial support mandate in the marketing authorisation and in NICE guidance on nalmefene. Going further still, Selincro-based treatment is being (not by Lundbeck) sold to patients on the basis solely of an "online consultation".

NICE seemed unmoved by the criticism: "Our appraisal process for nalmefene thoroughly interrogated the evidence base," said Carole Longson, director of the NICE Centre for Health Technology Evaluation, "and, as is the standard with all our appraisals, we engaged with and took into account submissions from a multitude of stakeholders. When presented with the evidence, including the analysis of the clinical studies, the independent committee concluded that there was sufficient evidence to recommend nalmefene in specific circumstances."

It's in the marketing

It is important to recognise that the innovation in Selincro is not nalmefene nor its use in the treatment of alcohol dependence, but its market re-positioning by Danish pharmaceutical company Lundbeck. The effect could be to break open a very large new market with a product which appeals to millions of heavy drinkers and offers doctors something concrete and familiar – prescribing a medication – they can do with patients who do not need detoxification and are unwilling to commit to abstinence, advantages lent Selincro less by a distinct pharmacology than by distinctive testing and marketing.

It was Lundbeck's marketing infrastructure which led original manufacturer Biotie to sell the company global development and commercialisation rights to the compound for 94 million Euros plus milestone payments and royalties on sales: "Lundbeck's specialist marketing force and its long-established relationships with prescribers in the relevant therapeutic areas will be important in driving a successful launch and maximizing the market potential for nalmefene."

Based on studies set up to evaluate it within these parameters, the product targets heavy drinkers who are nevertheless not physically dependent. According to Britain's prescribing guide, nalmefene is indicated for the "reduction of alcohol consumption in patients with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms, and who do not require immediate detoxification". Without the requirement that patients experience withdrawal symptoms when they stop drinking, and in contexts where specialist diagnostic tests for dependence are the exception, this formula lends itself to elastic interpretation, though the marketing authorisation was more precise.

The treatment itself is undemanding: it does not require abstinence or daily pill-taking, and allows the patient to decide whether that day they want to take the pill to moderate anticipated drinking, or leave themselves free to drink unrestrained by medication. Given this regimen, it would seem to make no sense to require administration of the drug to be supervised by family or other associates to ensure the patient takes the pills every day, eliminating that barrier to its applicability. Because the efficacy studies tested it accompanied by brief psychosocial support focused on encouraging use of the medication, this is how the drug has been authorised to be used, demanding little of the patient and their clinicians compared to fully-fledged therapies.

In the form of the unprovable belief that the patient drank less than they would have done had they not taken the pill, success for both prescriber and patient can be fudged in a way abstinence cannot. On days when the patient decides to take the pill, presumably they will already have been motivated to moderate their drinking and made a decision to do so. With or without the medication, motivation and resolution might have resulted in drinking less than on other occasions. Even when the 'medication' was an inactive placebo, in a US naltrexone trial, "on days when individuals took a tablet ... they tended not to drink heavily".

Despite being prescribed a medication, Selincro patients are in a better position to maintain a non-'alcoholic' identity than physically dependent drinkers treated in alcohol clinics because of the targeting of the medication and because the 'as needed' approach does not treat them as if they are 'out of control'.

Above all, the company has positioned Selincro so that it does not compete in intended recipients, usage and effects with the much cheaper naltrexone products, and has never tested whether naltrexone might be just as good in this role.

The appeal of Selincro was identified by the US *Newsweek* magazine in an article titled, "A pill could help alcoholics and let them drink in moderation", featuring the caption, "A new drug lets you drink without becoming a drunk." Two sides of the same coin, both the potential market and the potential public health benefits were highlighted: "Alcohol is one of the most dangerous drugs in the world ... yet data show a massive treatment gap when it comes to alcoholism. An estimated 17 million Americans have an alcohol-use disorder; nearly 4 million have a dependence, and yet only 1 million are in treatment. At most, 300,000 take medication." In Britain it seems nalmefene is being promoted heavily for use in

are in treatment. At most, 300,000 take medication." In Britain it seems nalmefene is being promoted heavily for use in primary care, which has the largest market of potential patients and prescribers.

Some of the product's marketing advantages were in 2011 promoted to Lundbeck's investors and were among the reasons why the company was looking to Selincro to make a substantial contribution to restoring flaggi ng profits as patents on older products expired and sales plummeted due to competition from generic products. "The company needs its new products to gain momentum quickly", commen ted *Pharmaceutical Industry News*.

So central was Selincro to this imperative that when in 2013 the company appointed a new vice president for global pricing and market access, her "most pressing task" was described as leading the launch of Selincro in the wake of European authorisation. In 2014 the company said among its key priorities was to increase revenue growth from new products, including Selincro. Though still a relatively small contributor, European authorisation had propelled Selincro to the company's fastest growing product, its revenue increasing by 520%. Since then, Lundbeck may have taken its foot of the Selincro pedal. An announcement in August 2015 of 1000 expected job losses out of 6000 staff in the attempt to regain profitability did not mention Selincro among the products on which the restructured company now intended to focus.

In England it was not until after NICE approved nalmefene in 2014 that sales – though still tiny in comparison to all alcohol medications – climbed noticeably above zero. Out of nearly 200,000 prescriptions for alcohol medications in 2015, 4400 were for nalmefene. However, its higher price (averaging £63 per item compared to £18 for acamprosate and £22 for disulfiram) meant it accounted for a greater – though still small – proportion of spending on alcohol medications.

The importance of avoiding generic competition

Most prominent (1 2) among Lundbeck's products suffering from generic competition was the antidepressant escitalopram, which Lundbeck markets as Cipralex. Selincro was meant to help plug the resulting revenue gap, a role which Cipralex had itself played several years earlier when it had been marketed to supersede citalopram, then threatened by generic competitors.

How Lundbeck and its competitors handled that process resulted in 2013 in Lundbeck paying a 93.8 million euro fine imposed by the European Commission after a finding of anti-competitive practice. The Commission discovered that in 2002 Lundbeck had paid companies manufacturing generic competitors to "stay out of its market and delay the entry of cheaper medicines". "Agreements of this type directly harm patients and national health systems, which are already under tight budgetary constraints," said the Commission's vice-president in charge of competition policy.

The Commission&rsquo ;s investigation discovered that perhaps the greatest benefit from delaying the entry of generic forms of citalopram was to extend the "window of opportunity" to replace the medication with new and still patent-protected Cipralex before the generics had gained a foothold in the market and brought prices down. If patients could be become settled on Cipralex before the generics came in, they would, the company thought, be unlikely to switch.

In 2013 Lundbeck appealed against the ruling, starting a process which could they say take six years.

There is no competition to Selincro in the form of generic nalmefene, but there might be in the form of generic naltrexone if medical regulators and national guidance placed it in the same clinical ball park as the newer product. As with Cipralex and before it citalopram, the effect would undoubtedly be to substantially constrict the market for Selincro and its ability to help elevate Lundbeck out of the financial dip caused by the expiry of patent protection on its older medications.
