Nalmefene for the treatment of alcohol dependence: a mixed-methods study of primary care prescribing patterns, pharmaceutical marketing and other influences

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Abstract

Background: Nalmefene is the first pharmacotherapy to be licensed for the reduction of alcohol consumption in patients with alcohol dependence. Marketed mainly for prescribing in primary care, the evidence supporting its efficacy and use in this setting remains contested. This thesis aims to describe and understand patterns of, and influences on, nalmefene prescribing in UK primary care.

Methods: A mixed-methods study including (1) a quantitative analysis of prescribing data; (2) a qualitative documentary analysis of nalmefene marketing; and (3) semi-structured interviews (*n*=19) with alcohol treatment and policy professionals.

Findings: (1) Nalmefene prescribing in UK primary care was low, apart from a temporary increase after nalmefene was recommended by the National Institute for Health and Care Excellence (NICE) in 2014, and prescribing was poorly aligned with licensing conditions; (2) An extensive range of marketing activities for nalmefene was undertaken by the pharmaceutical company, Lundbeck, creating opportunities to influence nalmefene uptake in UK alcohol treatment; (3) Whilst marketing activities may have garnered some support for nalmefene, there remained substantial barriers to its use, including poor compatibility with current models of alcohol treatment, and a lack of skills, resources and confidence in primary care to treat alcohol dependence.

Conclusion: Despite limitations in existing evidence, nalmefene marketing activities helped generate support for its use in alcohol treatment in the UK. Despite this, several barriers to its use meant that uptake in UK primary care remained low. Alcohol treatment policy should be underpinned by robust evidence and free from commercial influence. The introduction of nalmefene into UK prescribing had neither of these features. Among the implications for future research and policy is a need to support publically-funded research and to engage primary care professionals in developing effective interventions and supporting them to deliver these.

List of outputs arising from thesis

Sharp, C. (2017) Drugs for the treatment of alcohol dependence: insufficient evidence. Guest blog for the online newsletter 'Alcohol Policy UK'. 23 October 2017. See http://www.alcoholpolicy.net/2017/10/drugs-for-the-treatment-of-alcohol-dependence-insufficient-evidence.html.

Sharp, C. (2018) Nalmefene prescribing in the UK: Patterns and influences: Methodology. Presentation at the New Directions in the Study of Alcohol Group (NDSAG) 2018 Early Career Researcher Symposium, Sheffield, 6th June 2018.

Sharp, C. (2018) Profiling nalmefene use and patients using GP prescribing data: A descriptive retrospective cohort study using the Clinical Practice Research Datalink (CPRD). Presentation at the Scottish Alcohol Research Network PhD Symposium "Enlightened new alcohol research" (a satellite of the 8th European Alcohol Policy Conference), Edinburgh, 19th November 2018.

Understanding how the alcohol dependence drug nalmefene has been used in the UK: analysis using primary care prescribing data. Presentation at the Society for the Study of Addiction (SSA) 2019 PhD Symposium, Newcastle, 6th November 2019.

Sharp, C. (2021) A qualitative documentary analysis of UK-based marketing activities for nalmefene, a drug for alcohol dependence. Presentation to the Institute for Social Marketing and Health, University of Stirling, 17th May 2021.

Contribution to teaching materials for an online module (Alcohol Use: Policies and Interventions) for an MSc in Substance Use at the University of Stirling. I provided materials, slides and an audio recording for a lecture on pharmacological treatment for alcohol problems (January 2020).

I have drafted a paper with my academic supervisors (A qualitative documentary analysis of UK-based marketing activities for nalmefene, a drug for alcohol dependence), which is planned for submission to the online journal *PLoS ONE* in July 2021.

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Ethical approval

The studies within this thesis have been approved by University of Stirling NHS Invasive or Clinical Research (NICR) Committee (NICR 16/17 – Paper No. 71 and NICR 18/19 – Paper No. 033) and the Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee (ISAC) (Protocol 17_120R).

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Abbreviations and definitions

ABI	Alcohol brief intervention
ABPI	Association of the British Pharmaceutical Industry
AHM	Alcohol Harm Map
AIM	Alcohol Impact Model
Alcohol dependence	Characterised by craving, tolerance, pre-occupation with alcohol and continued drinking despite experiencing harmful effects
AUD	Alcohol use disorder (encompasses harmful drinking or alcohol dependence)
CBT	Cognitive Behavioural Therapy
CCG	Clinical Commissioning Group (Responsible for commissioning health services in a local area in England)
COI	Conflict of Interest
CPD	Continuing Professional Development
CPRD	Clinical Practice Research Datalink (a database of anonymised patient records from UK primary care)
DRL	Drinking Risk Level (WHO High DRL is > or = 60g alcohol per day for men, and > or = 40g alcohol per day for women)
EMA	European Medicines Agency (agency responsible for approving and licensing new medicines for use EU countries)
ERG	Evidence Review Group (an independent group appointed by NICE to assess nalmefene evidence on their behalf)
GP	General Practitioner
Harmful drinking	Harmful use is described as a pattern of drinking that is already causing damage to health (either physical or mental).
Hazardous drinking	Hazardous use is described as a pattern of drinking that carries a risk of harmful consequences (both health and social) to the drinker.
HDD	Heavy Drinking Day (a day with alcohol consumption of 60g or more for men and 40g or more for women)
ICP	Integrated Care Pathway (outlines the stages in the care of patients with a specific condition)

ISMH	Institute for Social Marketing and Health (University of Stirling)
KOL	Key opinion leader
Licensing conditions	These are the conditions included in a drug's licensing, and describe the patient group and conditions in which a drug should be prescribed. For nalmefene they are: patients with alcohol dependence, who are drinking at a high drinking risk level (DRL), without physical withdrawal symptoms and who do not need immediate detoxification. It should only be given to patients who continue to drink at a high DRL 2 weeks after an initial assessment, and all patients should receive continuous psychosocial support alongside nalmefene treatment.
MET	Motivational enhancement therapy
NHS	National Health Service
NICE	National Institute for Health and Care Excellence (provides evidence-based guidance and advice to health, public health and social care practitioners)
RCT	Randomised controlled trial
SMC	Scottish Medicines Consortium (provides advice to the NHS in Scotland about the value for patients of newly licensed medicines)
TA	Technology Appraisal (TAs determine whether a medicine should be funded by the NHS, based on its cost-effectiveness)
TAC	Total Alcohol Consumed (grams/day)
WHO	World Health Organisation

1 INTRODUCTION AND BACKGROUND

The focus of this thesis is on nalmefene, a pharmacological treatment for alcohol dependence. It is an opioid receptor antagonist which acts on the brain, and is thought to reduce the urge to drink (Mann et al., 2013). In March 2013, Lundbeck, the pharmaceutical company who licence the drug, received approval from the European Medicines Agency (EMA) to market it in the EU (European Medicines Agency Committee for Medicinal Products for Human Use, 2012). Nalmefene was subsequently approved for use in the NHS in Scotland by the Scottish Medicines Consortium (SMC) in September 2013 (Scottish Medicines Consortium, 2013). In November 2014, nalmefene was recommended by the UK National Institute for Health and Care Excellence (NICE) for the reduction of alcohol consumption in adults drinking at high-risk levels[1] who have been diagnosed with alcohol dependence (NICE, 2014a).

This chapter aims to provide some background to the study. Understanding the rationale for establishing interventions to address alcohol problems is important, and Section 1.1 outlines the nature and extent of alcohol harms to health and society. Before discussing nalmefene treatment, it is useful to understand where nalmefene fits in relation to other available approaches to addressing alcohol harms. Debates and challenges relating to these approaches are covered in Section 1.2, followed by an outline of the approaches themselves and the evidence for these (Section 1.3). The rationale for this study is presented in Section 1.4, followed by the study aims and research questions (Section 1.5). Finally, the structure of the thesis is presented (Section 1.6).

1.1 The nature and extent of alcohol harms

1.1.1 Harms to health and society

Alcohol can harm individuals and societies. Its direct impacts on health are well-documented. On a global level, harmful use of alcohol (see Abbreviations and definitions) is one of the key causes of death and illness, accounting for 5.3% of deaths worldwide (WHO, 2018a). It is one of the top five risk factors for disease, disability and death throughout the world (WHO, 2011; Lim et al., 2012), and the leading risk factor for these conditions among those aged 15 to 49 (WHO, 2014). In the UK, alcohol is a leading risk factor for ill-health, disability and

[1] Defined as alcohol consumption of 60g or more per day for men and 40g or more per day for women (WHO, 2000).

premature death across all age groups (Public Health England, 2016). It accounted for almost a tenth of registered deaths among 40- to 44-year-olds in the UK (Office for National Statistics, 2019). Hospital admissions data suggest that, in England, an estimated 7% of admissions in 2015/16 were related to alcohol[2] (National Statistics, 2017). In Scotland, it is estimated that 6.4% of individuals admitted to hospital at least once during 2015 were there due to alcohol consumption (Tod et al., 2018).

A range of health conditions have been associated with alcohol consumption. It is a causal factor for over 200 disease and injury conditions, including neuropsychiatric conditions, gastrointestinal disorders, liver cirrhosis, cardiovascular disease (CVD) and cancers (WHO, 2014, 2018a). Even low levels of alcohol consumption are a risk factor for cancer of the mouth and throat and gullet, and for breast cancer in women (Committee on Carcinogenicity, 2015), with moderate and heavy drinkers being at increased risk of a range of cancers (Bagnardi et al., 2015). Alcohol consumption has also been associated with mental health disorders. A fifth of alcohol-related hospital admissions are for mental and behavioural disorders[2] (Burton and Marsden, 2016). Common comorbid mental health disorders include depression and anxiety (NICE, 2011; Gimeno et al., 2017).

Whilst there is a wealth of evidence on the harmful effects of alcohol on health, there is also an ongoing debate about whether alcohol consumption can be a protective factor for some health conditions, including CVD. Many studies have reported negative consequences of heavy drinking on CVD (Rehm et al., 2004; Corrao et al., 2000), and almost half of UK alcohol-related hospital admissions are accounted for by CVD[2] (Burton and Marsden, 2016). Others have reported a 'protective effect' for alcohol based on the finding that CVD risk is lower for light to moderate drinkers relative to non-drinkers (Rehm et al., 1997; Hines and Rimm, 2001; Agarwal, 2002). This phenomenon is known as the 'j-shaped curve' due to the shape of the curve derived when alcohol consumption is plotted against risk of mortality from CVD (Holmes et al., 2016). There appears to be a lack of consensus on this issue, and studies continue to either support (Bell et al., 2017) or refute (Holmes et al., 2014; Stockwell et al., 2016) the claim that alcohol can have a protective effect. Some suggest that this protective effect may only apply in older age groups, and women in particular (Holmes et al., 2016).

[2] Based on a broad measure, where an alcohol-related disease, injury or condition was either the main reason for admission or was a secondary diagnosis.

Differences in level of risk among non-drinkers and light to moderate drinkers may also be explained by confounding factors, including health, social and lifestyle factors rather than alcohol consumption (Naimi et al., 2005; Chikritzhs et al., 2009; Holmes et al., 2016). In 2015, The Health Evidence Expert Group concluded that there is no justification for recommending alcohol consumption on health grounds, or for starting to drink alcohol for these reasons (Department of Health, 2016).

Alcohol has wider impacts on individuals, others around them, and society in general. The negative socioeconomic consequences of drinking for individuals can include loss of earnings, unemployment, family problems, social problems, crime and violence, stigma and problems accessing health care (Babor et al., 2010; Henkel, 2011; WHO, 2014). The health and wellbeing of a range of other individuals, including family members and strangers, can be negatively affected by someone else's drinking (WHO, 2014). Alcohol has also been associated with violent crime (Wright, 2017) and intimate partner violence (Foran and O'Leary, 2008; Flatley, 2015). Children are particularly vulnerable as a result of parental drinking (Manning et al., 2009; Mariathasan and Hutchinson, 2010; Rossow et al., 2016). The economic impact of alcohol-related harms on society is considerable, involving expenditure from across the range of public services, including health, criminal justice, local government and schools (University of Stirling, 2013). Annual costs to individuals and society have been estimated at £7.5 billion in Scotland (Johnston et al., 2012) and up to £55.1 billion in England (Lister et al., 2008).

1.1.2 Who is most at risk from alcohol harms?

Risk of alcohol-related harm is associated with how alcohol is consumed (for example, volume and frequency of consumption) and by whom (Burton and Marsden, 2016). Individuals who drink more heavily are most at risk of alcohol-related disease or injury (Rehm et al., 2010, 2017; Burton and Marsden, 2016). However, drinking at low levels is associated with certain types of cancer, as mentioned above (Committee on Carcinogenicity, 2015). Particular groups of the population are more vulnerable to alcohol-related harms, including women, children and young people, and those from lower socioeconomic groups (Burton and Marsden, 2016; WHO, 2018a). Despite drinking at similar or lower levels to more affluent groups, those from lower socioeconomic groups experience more harm from alcohol (a phenomenon known as the 'alcohol harm paradox') (Jones et al., 2015). Possible

explanations underpinning this may relate to patterns of drinking in this group, as well as health factors (Burton and Marsden, 2016).

1.1.3 Prevalence of harmful levels of alcohol use in the general population

This study will only report on the prevalence of harmful alcohol use at the UK level, as the UK is the focus of the thesis and of the data included within it. For international-level data, a key source is the WHO Global Status Report on Alcohol and Health (WHO, 2018a). Measures of alcohol consumption in the UK general population are derived from two key sources – self-report data from surveys, and alcohol sales data. Population health surveys collect self-reported unit consumption data that can be used to estimate the proportion of the population drinking at various risk levels. According to the 2019 Health survey for England, 30% of men and 15% of women drank at 'risky' levels (defined as drinking in excess of the UK guideline limit of 14 units of alcohol per week). An estimated 25% of men and 12% of women drank at 'increasing risk' levels (in men, between 14 and 50 units per week and in women, between 14 and 35 units per week), and 5% of men and 3% of women drank at 'higher risk' (in men, more than 50 units a week and in women more than 35 units a week) (Bankiewicz and Robinson, 2020). In Scotland, drinking above the weekly limit of 14 units is described as 'hazardous or harmful drinking', and the 2019 Scottish Health Survey reports that 32% of men and 16% of women drank at this level (Shields, 2020); the equivalent figures for Wales and Northern Ireland are 25%, 12% and 26% and 9%, respectively (Welsh Government, 2020; Corrigan and Scarlett, 2020).

UK population surveys have also provided estimates of harmful or dependent drinking, based on scores derived from the Alcohol Use Disorders Identification Test (AUDIT) screening tool (Babor et al., 1992), with scores of 16 and over indicating harmful or dependent drinking. In England, estimates from the Adult Psychiatric Morbidity Survey suggest 4.4% of men and 1.8% of women are drinking at this level (Drummond et al., 2016). Equivalent figures from the Scottish Health Survey are 3% of men and 1% of women (Shields, 2020).

Self-report surveys, while offering insights into drinking patterns among different sub-groups of the population, are thought to account for only around half of the estimated consumption captured by alcohol sales data (Beeston et al., 2016). This is due to under-reporting by survey respondents or because survey sampling methods may not capture the heaviest drinkers (Bellis et al., 2009). Alcohol sales data suggest a much higher rate of consumption. For example, in Scotland, 9.9 litres of alcohol per adult aged 16 and over were sold in 2019,

equating to 19.1 units per adult per week; the equivalent figure for England and Wales was 9.1 litres (17.5 units per adult per week) (Giles and Richardson, 2020). Whether the discrepancy between sales and survey data is due to more people drinking or because more units are being consumed by the heaviest drinkers is not known.

Although both alcohol sales data and survey data suggest a decline in alcohol consumption since 2005, this has not been matched by reductions in levels of alcohol-related harm over the same time periods. Increases in alcohol-related hospital admissions have continued beyond periods of declining consumption, suggesting that there is a lag whereby the benefits of any reduction are yet to be realised (Green et al., 2017). The nature of this relationship between alcohol consumption and alcohol harm trends has been described as being complex and due in part to varying consumption trends between types of drinker and between sub-groups of the population (Holmes et al., 2019).

1.2 Addressing alcohol harms – debates and challenges

Before describing the key approaches taken to address alcohol harms, it is important to understand some of the broader perspectives and debates which underpin them. These are discussed in relation to the focus of interventions (population versus individual level); defining and diagnosing problem drinking (binary versus continuum beliefs); treatment goals (abstinence versus controlled drinking); and theories of problem drinking.

1.2.1 Population versus individual level focus

ldentifying policies and measures which have the potential to reduce alcohol consumption and/or related harms has been the focus of considerable attention by governments and other organisations (Scottish Government, 2009; Babor et al., 2010; University of Stirling, 2013; Burton and Marsden, 2016; WHO, 2018a). Such interventions vary widely in their approach, focus and target population (Babor et al., 2010). Two broad categories describe the range of policies and interventions which have been used – those which aim to reduce consumption and harms in the whole population, and those which focus on helping individuals with higher-risk drinking (Babor et al., 2010). The relative merits of health strategies aimed at whole populations versus ‘high-risk’ groups of the population have been discussed by Geoffrey Rose (2001), who concludes that population measures which attempt to control or remove the underlying causes of a disease offer the greatest potential health benefits to populations (whilst the benefits to individuals may only be subtle). In relation to alcohol,

whilst those drinking at dependent levels experience more harm relative to other drinkers, it is the larger group, those who are drinking at hazardous or harmful levels, but may not be experiencing obvious alcohol harms or dependence, who account for the largest share of alcohol-related problems in the population, a phenomenon known as the 'prevention paradox' (Kreitman, 1986; O'Dwyer et al., 2019).

Despite their potential benefits for population health, implementing population-wide approaches is challenging. Firstly, they may not be viewed as acceptable, given that the observable benefits for individuals are small (the 'prevention paradox') (Rose, 2001) and because the public tend to favour measures perceived to target 'other' drinkers (such as treatment for dependency) over those affecting all drinkers (University of Stirling, 2013). For example, one factor behind public opposition to minimum unit pricing, a population measure introduced in Scotland, was a perception that it 'punishes' everyone for what some drinkers do (Sharp et al., 2014). Secondly, global factors may hinder the implementation of some population measures, including international controls and trade agreements which can affect taxation and pricing measures and the global reach of online alcohol advertising, which may be able to circumvent restrictions implemented in individual countries (Babor et al., 2010; Hellman et al., 2020).

In addressing alcohol problems, no one single solution is recommended (Babor et al., 2010; Martineau et al., 2013). Instead, a range of interventions drawn from both population and individual approaches are needed (Edwards, 1997; University of Stirling, 2013).

1.2.2 Defining and diagnosing problem drinking (binary versus continuum beliefs)

Different approaches have been taken to categorise problem drinkers into specific groups, and these appear to be continually shifting. The approach used has implications for the diagnosis, investigation and treatment of alcohol problems (Hasin et al., 2013). A common approach has been to distinguish between 'harmful drinking' and 'alcohol dependence'. This has been the adopted approach to diagnosing alcohol use disorders (AUDs) in the two main international classification systems. In the WHO International Classification of Diseases (ICD-10), "*harmful use*" is described as drinking that results in damage to the physical or mental health of the user (WHO, 1992, p. 74) whilst alcohol dependence is defined as:

> *A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong*

> *desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.*

The fourth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994) divides individuals with AUDs into those with 'alcohol abuse' and those with 'alcohol dependence'. DSM definitions have been used to define inclusion criteria for participants in alcohol treatment studies (Hasin, 2003), including in the nalmefene clinical trials, which used DSM-IV criteria to assess for alcohol dependence (Mann et al., 2013). However, the latest iteration of the DSM (DSM V) attempts to reflect new ways of thinking about how alcohol problems should be defined (American Psychiatric Association, 2013). The new classification places individuals on an 'AUD' continuum, ranging from 'mild' to 'severe' based on the number of criteria they possess, as outlined in Table 1 (National Institute on Alcohol And Alcoholism, 2013). Continuum approaches recognise a broad spectrum of alcohol problems and may be helpful in identifying all individuals who might benefit from an intervention (Hasin et al., 2013). Continuum beliefs about alcohol problems may also help individuals recognise their drinking problems (Morris et al., 2020). Classifying diseases based on a continuum approach can potentially widen the pool of people becoming eligible for medical treatment (Healy, 2006; Hardoon et al., 2013; Allen, 2016), although this also presents a risk of 'over-medicalisation' of some problems, which could otherwise have been addressed without medical treatment, and possibly at less cost to services (Parens, 2013; Allen, 2016).

Table 1: Comparison of DSM IV and V classifications for alcohol dependence

DSM-IV Criteria **ANY 1 OF 1 TO 4 = Alcohol abuse** **ANY 3 OF 5 TO 11 = Alcohol Dependence**	**DSM-V Criteria** **2 to 3 symptoms = Mild dependence** **4 to 5 symptoms = Moderate dependence** **6+ symptoms = Severe dependence**
In the past year, have you:	In the past year, have you:
1. Found that drinking—or being sick from drinking—often interfered with taking care of your home or family? Or caused job troubles? Or school problems?	1. Had times when you ended up drinking more, or longer, than you intended?
2. More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?	2. More than once wanted to cut down or stop drinking, or tried to, but couldn't?
3. More than once gotten arrested, been held at a police station, or had other legal problems because of your drinking? **This is not included in DSM-5**	3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects. (See DSM-IV, criterion 9.)
4. Continued to drink even though it was causing trouble with your family or friends?	4. Spent a lot of time drinking? Or being sick or getting over other after effects? **New to DSM-5**
5. Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?	5. Found that drinking—or being sick from drinking—often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
6. Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?	6. Continued to drink even though it was causing trouble with your family or friends?
7. Had times when you ended up drinking more, or longer, than you intended?	7. Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
8. More than once wanted to cut down or stop drinking, or tried to, but couldn't?	8. More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
9. Spent a lot of time drinking? Or being sick or getting over other after effects?	9. Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
10. Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?	10. Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
11. Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?	11. Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?

Source: National Institute on Alcohol and Alcoholism, 2013

To add to the continuing debate about classifying alcohol problems, the recently published revised ICD classification (ICD-11) has moved away from a continuum approach, and instead divides AUDs into two categories: 'harmful use', and 'alcohol dependence syndrome' (WHO, 2018b; Lange et al., 2019). Critics of the new ICD-11 approach have cited various problems, including: that it diverges significantly from the new DSM system; that it may not capture alcohol dependence which is at the milder end of the spectrum; it is less relevant to primary care; and, similar to the other classifications, does not incorporate any measure of the level of alcohol use (Carvalho et al., 2019; Rehm et al., 2019). It is argued that heavy level of use over time is a more useful indicator of the majority of health and social problems associated with substance misuse (Rehm et al., 2013a).

In the UK, the NICE guidelines on AUDs (NICE, 2011 p. 4) use definitions of harmful drinking and alcohol dependence which align with those in ICD-10 and DSM-IV. Harmful drinking (also referred to in the guidelines as 'high-risk' drinking) is defined as:

> *a pattern of alcohol consumption causing health problems directly related to alcohol. This could include psychological problems such as depression, alcohol-related accidents or physical illness such as acute pancreatitis.*

Alcohol dependence is defined as being:

> *characterised by craving, tolerance, a preoccupation with alcohol and continued drinking in spite of harmful consequences (for example, liver disease or depression caused by drinking). Alcohol dependence is also associated with increased criminal activity and domestic violence, and an increased rate of significant mental and physical disorders.*

However, a continuum approach to defining alcohol dependence is also supported in the guidelines:

> *Although alcohol dependence is defined in ICD-10 and DSM-IV in categorical terms for diagnostic and statistical purposes as being either present or absent, in reality dependence exists on a continuum of severity. However, it is helpful from a clinical perspective to subdivide dependence into categories of mild, moderate and severe.*

The guidelines also state that people with moderate and severe levels of dependence will require assisted alcohol withdrawal.

1.2.3 Treatment goals – abstinence versus controlled drinking

A key debate in the alcohol treatment field has concerned whether individuals with alcohol dependence can safely manage to control their drinking. The history of this debate has been covered elsewhere in detail (Roizen, 1987; Drug and Alcohol Findings, 2021). In summary, the mainstream view in the alcohol treatment field had been that abstinence was the only appropriate treatment goal for patients with alcohol dependence, a view held for decades. During the 1960s and '70s, research emerged which reported that some patients with alcohol dependence could safely reduce their drinking and maintain lower levels; however, these findings were strongly contested at the time (see Drug and Alcohol Findings, 2021). Subsequent research has supported the use of controlled drinking in patients with alcohol dependence (Hodgins, 2005; van Amsterdam and van den Brink, 2013; Henssler et al., 2020).

Previous research has also raised awareness of the role of treatment goals more widely in influencing patient outcomes from alcohol interventions, specifically, that patient preference of treatment goal (whether abstinence or controlled drinking) is a key factor in achieving the desired goals (Adamson et al., 2010), and that there are benefits when the patient and therapist make shared decisions about treatment goals (Joosten et al., 2011; van Amsterdam and van den Brink, 2013). As for which groups of patients are most suitable for controlled drinking, it is suggested that it may be more beneficial for patients with lower levels of alcohol dependence (Hodgins, 2005). This has been the position in the NICE guidelines (2011), which recommend that abstinence is likely to be the appropriate treatment goal for most patients with alcohol dependence, and that controlled drinking may be more suitable for harmful drinkers or those with mild dependence. However, a recent meta-analysis, which reported that controlled drinking was non-inferior to abstinence in alcohol-related outcomes, also reported that this was not moderated by severity of alcohol dependence (Henssler et al., 2020). Despite an increasing acceptance of controlled drinking as a viable treatment goal in many EU countries (Rehm et al., 2013b), abstinence may still be the dominant treatment approach in specialist alcohol services (Witkiewitz and Marlatt, 2006; Klingemann, 2016; Goh and Morgan, 2017; Witkiewitz et al., 2017a).

1.2.4 Theoretical perspectives of problem drinking

Another debate in the alcohol field relates to the nature and causes of problem drinking, including whether problem drinking should be thought of as a disease in various senses. A common 'disease model' theory is based on the premise that addiction is a disease of the brain (Leshner, 1997; Volkow et al., 2016). A key aspect of the theory relates to choice – individuals who are addicted to a substance are said to undergo changes in their brain functioning, which leaves them with no control over whether they use the substance or not (Leshner, 1997; Wiens and Walker, 2015; Volkow et al., 2016). This brain disease model approach has also been linked with a preference for abstinence as the most appropriate treatment goal in addressing problem drinking (Levine, 1985).

This view became dominant in alcohol treatment in the 1930s and '40s (Levine, 1985) and was since adopted by many influential institutions, including the American Medical Association, the WHO, and the US National Institute on Alcohol Abuse and Alcoholism (Wiens and Walker, 2015). Proponents of the disease model approach hoped that it might help change public perceptions of addiction and therefore reduce the stigma associated with problem drinking (individuals would not be blamed for their alcohol problem if it was classed as a disease over which they had no control) and help to establish rights to medical treatment for problem drinkers (Jurd, 1992). It would also highlight the perspective that treatment was essential in helping individuals overcome their addiction problem (Drug and Alcohol Findings, 2017).

A critic of disease model framing, Professor Nick Heather, questions the utility of framing alcohol problems in this way and the current relevance of some previously purported benefits of the approach, including better access to treatment and more sympathetic attitudes to problem drinkers (Heather, 1992, 2017). Research in this area has raised doubts about whether disease model thinking reduces stigma or feelings of shame (Schomerus et al., 2014; Hall et al., 2015; Wiens and Walker, 2015). Concerns raised about the potential risks of disease model framing include that it weakens personal responsibility for addressing alcohol problems; it may hinder problem recognition; that it could impose abstinence goals on individuals who wish to reduce rather than stop their drinking; that it focuses efforts (research, treatment and policy) on addressing the needs of those with the most severe alcohol problems; and, by default, deflects attention away from measures targeted towards

the large pool of other drinkers, including population measures (Heather, 1992; Hall et al., 2015; Wiens and Walker, 2015; Heather et al., 2018; Morris et al., 2020).

1.3 Current approaches to addressing alcohol problems

1.3.1 Population-level approaches

Population-level approaches to addressing alcohol problems are based on the theory that reducing population consumption of alcohol will result in a reduction in alcohol-related harms (Elder et al., 2010; Wagenaar et al., 2010). Whilst this idea is contested (Sobell and Sobell, 1995; Single, 1996), there is also evidence to suggest that such policies have been successful, especially regulatory measures to control the availability and affordability of alcohol, and to tackle drink-driving (Martineau et al., 2013; University of Stirling, 2013). Less convincing evidence has been established for interventions based on self-regulation of alcohol marketing, voluntary codes of retail practice, and information and education initiatives (Babor et al., 2010; Martineau et al., 2013).

The main types of population measures are discussed below.

1.3.1.1 Fiscal measures

Taxation and price measures work on the assumption that reducing the affordability of alcohol will reduce demand for it, consequently leading to a reduction in consumption and related harms. There is convincing evidence that demand for alcohol responds to price changes (Wagenaar et al., 2009) and that increasing alcohol price or taxation reduces overall consumption of alcohol and related harms (Martineau et al., 2013). Evidence on minimum unit pricing of alcohol suggests that it can reduce alcohol consumption and related harms (Stockwell et al., 2012; Boniface et al., 2017); more recent evaluations, conducted following the implementation of the policy in Scotland, report reductions in alcohol sales (Robinson et al., 2020) and purchases (O'Donnell et al., 2019).

1.3.1.2 Regulating marketing

Exposure to alcohol advertising has been linked with increased drinking, especially among young people (Jernigan, 2006; Anderson et al., 2009; Smith and Foxcroft, 2009). Although there are restrictions on advertising content (mostly through industry self-regulation), these may not reduce the appeal of alcohol (Zwarun and Farrar, 2005) or its consumption (Nelson, 2010). Even where regulations are relatively strict, as in France, recent research indicates that

alcohol is nevertheless successfully promoted (Gallopel-Morvan et al., 2017; Purves and Critchlow, 2017).

1.3.1.3 Regulating availability

Availability refers to the ease or convenience of obtaining alcohol (Babor et al., 2010). There is good evidence that policies restricting the availability of alcohol can result in reduced consumption and associated harms (Anderson and Baumberg, 2006; Martineau et al., 2013). Examples include limiting the days and hours of alcohol sales (Middleton et al., 2010) and restricting the legal age of buying alcohol (Wagenaar and Toomey, 2002).

1.3.1.4 Reducing drink-driving

Drink-driving can cause health harms to drinkers and those around them (Taylor and Rehm, 2012). Enforcement policies have included breath testing and police patrols, drink-driving awareness campaigns and policies to lower the blood alcohol level for driving (Martineau et al., 2013). The evidence for these policies in reducing drink-driving incidents is strong (Martineau et al., 2013), and they are also viewed to be cost-effective (Burton and Marsden, 2016).

1.3.1.5 Information and education

Information and education campaigns, though commonly used to inform individuals about the risks of drinking, have had only mixed or limited success in reducing alcohol consumption or harms (Babor et al., 2010; Martineau et al., 2013). However, they can raise awareness of alcohol harms (Young et al., 2018) and may help secure some public support for other more successful approaches to reduce alcohol consumption (Fitzgerald and Angus, 2015). Including warning labels on alcohol products can increase public awareness of harms, but there is no evidence to support its effectiveness in reducing drinking (Babor et al., 2010; Miller et al., 2016). The labelling of tobacco products, by contrast, has had some success in encouraging change in smoking behaviour, and may offer insights for alcohol labelling (Wilkinson and Room, 2009).

1.3.1.6 Managing the drinking environment

These measures aim to improve the safety of drinking environments, such as pubs or clubs, and include toughened glassware, training for those serving alcohol, and wider policing and community interventions (Babor et al., 2010; Burton and Marsden, 2016). The evidence on

these is mixed (Martineau et al., 2013), showing only modest, if any, reduction in alcohol harms (Burton and Marsden, 2016).

1.3.2 Individual-level approaches

This section describes the key types of individual-level interventions available for people with a range of alcohol problems, and discusses the evidence for these. They are grouped into four key types: alcohol brief interventions, psychosocial therapies, mutual aid, and pharmacotherapy.

1.3.2.1 Alcohol brief interventions (ABIs)

The WHO manual on brief interventions for hazardous and harmful drinking[3] describes them as "*those practices that aim to identify a real or potential alcohol problem and motivate an individual to do something about it*" (Babor and Higgins-Biddle, 2001, p. 6). Although no formal definition exists, in the UK they have been described as:

> *a short, evidence-based, structured conversation about alcohol consumption with a patient/client that seeks in a non-confrontational way to motivate and support the individual to think about and/ or plan a change in their drinking behaviours in order to reduce their consumption and/or their risk of harm.* (Scottish Government, 2013, p. 1)

ABIs are typically delivered during a standard consultation by using a screening questionnaire to identify whether individuals are drinking at hazardous or harmful levels; those screening positive are given the opportunity to discuss their drinking (Moyer and Finney, 2015). The length of an ABI varies depending on client needs and practitioner time (Scottish Government, 2016). Simple brief interventions may only last a few minutes, whilst extended brief interventions tend to encompass longer (20–30-minute) structured therapies which are often repeated (Raistrick et al., 2006). ABIs are generally targeted towards individuals who have not been diagnosed with alcohol dependence, or who do not have an AUD (Raistrick et al., 2006), although some individuals with dependence may benefit (Blow

[3] Hazardous use is described as a pattern of alcohol consumption that carries a risk of harmful consequences (both health and social) to the drinker. Harmful use is described as a pattern of drinking that is already causing damage to health (either physical or mental) (Babor and Higgins-Biddle, 2001).

et al., 2009). In the UK, NICE (2011) guidelines recommend that brief advice be used as a first step for adults identified as drinking at hazardous or harmful levels, with an extended form of brief intervention recommended for those who do not reduce their drinking.

Evidence suggests that ABIs delivered in primary care can reduce alcohol consumption and related problems (Whitlock et al., 2004; Raistrick et al., 2006; Kaner et al., 2007; Jonas et al., 2012), although only certain groups of drinkers may benefit (Kaner et al., 2007; O'Donnell et al., 2014). Issues relating to the evidence for ABIs and how this translates across to real-world clinical practice have been raised (Raistrick et al., 2006; O'Donnell et al., 2014; McCambridge and Saitz, 2017). Barriers to effective implementation of ABIs include: attitudes towards alcohol use; a lack of organisational and structural support; a lack of clarity in who should take responsibility for addressing alcohol use; fears about jeopardising the professional/patient relationship; and pressures to deal with competing healthcare needs (Derges et al., 2017). However, there is evidence that ABIs, and even the act of screening alone, may serve to change drinking behaviour in some patients (Kypri et al., 2007; McCambridge and Day, 2008), and ABIs have been implemented across all four nations of the UK (Fitzgerald and Angus, 2015).

1.3.2.2 Psychosocial interventions

Psychosocial interventions aim to prevent, reduce or curtail alcohol consumption using a variety of behaviour change techniques, and can be delivered face-to-face or in other formats. They vary in intensity and length and use different approaches and theories (Raistrick et al., 2006). They can also be useful at different stages in the treatment journey, including at initial contact, to help individuals recognise that they have a problem or, later on, as a way of supporting other treatment, for example, in combination with pharmacotherapy (European Monitoring Centre for Drugs and Drug Addiction, 2016). NICE (2011) guidelines advise that these interventions should be offered to those drinking at harmful levels or those with mild alcohol dependence and that a combination of psychosocial interventions and pharmacotherapy should be considered for those with moderate or severe dependence.

There are numerous types of psychosocial interventions available to address alcohol problems, some for use with the individual, but others also involving family and friends. Those recommended by NICE include cognitive behavioural therapies (Ashton, 1999), social network and environment-based therapies (Copello et al., 2002), and, for those who have a partner willing to be involved in the treatment, behavioural couples therapy (Fals-Stewart et

al., 2004). Most of the key interventions belong to one of two key groups – those which employ motivational techniques, and those which are based on cognitive behavioural techniques (Raistrick et al., 2006). Table 2 outlines some of the key intervention types across both of these groups. This is not an exhaustive list, but covers a range of the most prominent approaches cited in the NICE (2011) guidance documents, a critical appraisal of international evidence on effectiveness of alcohol treatment (Raistrick et al., 2006) and some well-known studies of alcohol treatment (Ashton, 1999; UKATT Research Team, 2005). The table includes interventions that are used in both treatment and non-treatment-seeking populations.

Table 2: Psychosocial interventions

Intervention	Underlying principle and Aims	Content and Delivery	Evidence	Target group
Motivational interviewing (MI)	MI assumes that most individuals are capable of changing their behaviour by themselves once they become motivated to do so (Raistrick et al., 2006).	MI is defined by its originators (Miller and Rollnick, 2013, p.12) as "*a collaborative conversation style for strengthening a person's own motivation and commitment to change.*" MI is a commonly used form of less-intensive treatment, typically involving 1–4 relatively brief sessions (Raistrick et al., 2006).	A National Treatment Agency (NTA) review reported that, although MI is no more or less effective than other psychosocial approaches, it compares well with more intensive treatments, such as CBT and TSF (see below), offering a more cost-effective approach (Raistrick et al., 2006). A Cochrane review reported a greater reduction in substance misuse among individuals who received MI compared with no intervention. It also stated that MI was no more effective compared with other active treatments, treatment as usual and being assessed and receiving feedback (Smedslund et al., 2011).	MI tends to be targeted towards non-treatment-seeking individuals. NICE guidelines advise that it is used in extended brief interventions for individuals identified via screening as drinking at hazardous or harmful levels (NICE, 2010). A motivational intervention is recommended for all individuals with alcohol problems (NICE, 2011).
Motivational Enhancement Therapy (MET)	MET aligns with principles of motivational psychology. A form of MI, it aims to equip individuals to help themselves to achieve their goals, but also uses an analysis of assessment feedback gained from client sessions (Miller et al., 1999a).	Initial sessions cover structured feedback, future plans and motivation for change, with final sessions used to provide opportunities for the therapist to reinforce progress, encourage reassessment, and assess the process of change (Miller et al., 1999a).	MET was among the four most effective treatments found for the prevention of relapse in a Scottish review of psychosocial therapies (Slattery et al., 2003). The UKATT study (UKATT Research Team, 2005) reported that MET was equally as effective as the newly developed and more comprehensive SBNT (see below). It is considered effective for users with moderate alcohol dependence, assuming there is sufficient follow up provided (Raistrick et al., 2006).	Similar to MI, MET is also used in extended brief interventions for individuals drinking at hazardous or harmful levels (NICE, 2010).
Cognitive Behavioural Therapy (CBT)	CBT uses principles from social learning theory, in which problem drinking is viewed as a learned response to life's problems (Kadden et al., 2003). CBT aims to 're-programme' these learned responses by	Emphasis is on overcoming skill deficits and increasing ability to cope with high-risk situations that may lead individuals to relapse. Training aims to teach individuals to use coping methods rather than alcohol to deal	An NTA review of the research evidence concluded that CBT approaches offer the best chance of success and that the CBT therapies included in the Project MATCH study were equally but no more effective than MET or TSF (Raistrick et al., 2006).	CBT approaches are recommended by NICE for harmful drinkers and people with mild alcohol dependence (NICE, 2011).

	teaching cognitive coping strategies to deal with problems (Ashton, 1999).	with their problems (Kadden et al., 2003).		
Community Reinforcement Approach (CRA)	A type of CBT which uses social networks including family and work colleagues to reward clients who attain their goal (Raistrick et al., 2006). It aims to help individuals to stop drinking by eliminating positive reinforcement for drinking and enhancing positive reinforcement for sobriety (Miller et al., 1999b).	CRA uses a number of components including: increasing the client's motivation to stop drinking, starting a trial period of sobriety, analysing drinking behaviour, increasing positive reinforcement, rehearsing new coping behaviours, and involving the client's social networks (Miller et al., 1999b).	Studies suggest that patients given CRA have better outcomes than those receiving other forms of treatment (Hunt and Azrin, 1973; Smith et al., 1998). Hunt and Azrin (1973) reported that CRA patients did better on reduced drinking, more days of employment and greater social stability. CRA compared more favourably than the usual treatment provided in relation to reducing the number of drinking days (Roozen et al., 2004).	NICE guidelines recommend that social network and environment-based therapies are used to treat harmful drinkers and those with mild alcohol dependence (NICE, 2011).
Social Behaviour and Network Therapy (SBNT)	A CBT approach drawing on the individual's social networks including family and friends. It is based on the premise that individuals with drinking problems will be more successful in changing their behaviour if they have support from their social networks (Copello et al., 2002).	SBNT involves identifying and contacting network members, working to resolve issues the individual has with engaging their support, and working with the network to agree drinking goals and how to maintain them (Copello et al., 2002). NICE recommends that these therapies focus on alcohol-related problems and should usually consist of eight 50-minute sessions over 12 weeks.	The UKATT study found SBNT to be effective in reducing alcohol use and related harms (although it was no more or less effective compared with MET (UKATT Research Team, 2005).	As above.
Coping and Social Skills Training (CSST)	CSST recognises that many problem drinkers can find interpersonal relationships stressful and a cause of anxiety, and that this may influence their drinking behaviour (Raistrick et al., 2006).	The focus is on developing interpersonal and coping skills (Raistrick et al., 2006).	CSST was one of four cost-effective psychosocial treatments in a Scottish review (Slattery et al., 2003). Another review concluded that CSST was an effective treatment in those with moderate alcohol dependence, especially in those with poor social skills (Raistrick et al., 2006).	Treatment-seeking group
Couples and Family Therapy (CFT)	CFT approaches involve partners or family members on the assumption that an individual's substance misuse problems are associated in some way with family life. Family members are	NICE recommends that these therapies focus on alcohol-related problems and their impact on relationships and should usually consist of one 60-minute session per week over 12 weeks.	These approaches have shown to be effective treatment for users who have partners, where the partner is willing to participate (Raistrick et al., 2006). Marital and family therapies were among the four approaches identified in	NICE recommends that these types of therapies should be offered to harmful drinkers and people with mild alcohol dependence

	seen as having a crucial role in addressing these problems. (Fals-Stewart et al., 2004)		a Scottish review as being most effective in preventing relapse (Slattery et al., 2003).	who have a regular partner willing to participate in treatment therapy (NICE, 2011).
Behavioural Self Control Training (BSCT)	BSCT is a multi-component intervention aiming to teach skills that target controlled drinking as a treatment goal (Saladin and Santa Ana, 2004)	BSCT involves setting limits, self-monitoring of drinking, methods to control drinking or refuse alcohol, as well as systems for self-reward (Raistrick et al., 2006).	A meta-analysis of RCTs concluded that compared with no treatment and non-abstinence oriented interventions, BSCT for problem drinkers succeeded in reducing drinking and drinking-related difficulties in those with moderate to severe alcohol problems (Walters, 2000).	Treatment-seeking group, normally used where there is a goal of moderation (NICE, 2011).
Twelve-step facilitation (TSF)	This approach was developed within Project MATCH and is based on the same set of principles used in Alcoholics Anonymous (AA) (Nowinski, Baker and Carroll, 1999).	TSF involves getting individuals to accept that they have a disease, to work through the 12 steps from AA and to encourage attendance at AA meetings (Ashton, 1999). Sessions are highly structured, and include symptoms inquiry, encouraging AA participation, learning about the week's theme, and setting goals for AA participation for the next week (Nowinski, Baker and Carroll, 1999).	In Project MATCH, TSF was reported to be as successful as MET and CBT in relation to the study outcomes (percentage of days abstinent and drinks per drinking day). (Raistrick et al., 2006).	Treatment-seeking group

Two important large-scale studies about the effectiveness of psychosocial approaches in addressing problem drinking are the US Project Match study (Ashton, 1999), and the UK Alcohol Treatment Trial (UKATT) study (UKATT Research Team, 2005). Both reported that all interventions considered were successful in producing positive outcomes, and no single intervention was more or less successful than another in reducing drinking. Reasons for this have been debated, and suggested explanations include the common use of specific methods to encourage behaviour change and, in particular, the importance of the therapist and therapeutic relationship in obtaining good outcomes (Rogers, 1957; Ashton, 1999; Raistrick et al., 2006; Horvath et al., 2011).

1.3.2.3 Mutual aid groups

Mutual aid groups are peer-led interventions, where individuals with alcohol misuse meet to help themselves to recover from their problems. One well-known self-help group for alcohol problems is Alcoholics Anonymous (AA), founded in the US in 1935 to help individuals recover from alcohol dependence (Room and Greenfield, 1993). The AA approach is underpinned by a belief that alcohol dependence is both a spiritual and medical disease and that individuals with dependence should aim for abstinence (Nowinski et al., 1992). Evidence suggests that interventions using AA approaches can reduce alcohol consumption, achieve abstinence and reduce alcohol-related problems (Ferri et al., 2006). These approaches are considered to be both cost-effective and a good source of ongoing support (Raistrick et al., 2006), and guidelines from NICE (2011) recommend that professionals dealing with people seeking help for alcohol misuse should provide them with information about support networks and mutual aid groups such as AA.

1.3.2.4 Pharmacotherapy

Pharmacotherapeutic approaches for treating alcohol problems are long-established. Disulfiram, an aversion-therapy medication[4] has been used to treat alcoholism for over 60 years (Hald and Jacobson, 1948). Since then, increasing research on how processes in the brain react to alcohol use has led to the investigation and availability of a wide range of other drug treatments for alcohol problems (Wackernah et al., 2014). Table 3 describes the key

[4] Disulfiram acts indirectly to deter drinking by causing an unpleasant reaction when mixed with alcohol (Fuller and Gordis, 2004).

drug therapies approved for use in the UK to treat alcohol dependence (Acamprosate, Oral naltrexone, Disulfiram, and Nalmefene). Other emerging drugs not currently approved for treating alcohol dependence, but which have been the subject of recent research interest in this area (Lin, 2014; Wackernah et al., 2014), are also discussed.

Table 3: Drugs used in the treatment of alcohol problems

Drug name (brand name)	Therapeutic indications (from Summary of Product characteristics for each medicine)	Treatment goal in relation to alcohol problems	How it works	NICE recommendation
Acamprosate (Campral)	To maintain abstinence in alcohol-dependent patients. It should be combined with counselling.	Abstinence	Acamprosate is thought to stabilise the chemical imbalance in the brain resulting from alcohol withdrawal, by blocking the N-methyl-D-aspartate (NMDA) receptors and thereby reducing the effects that occur during early abstinence from alcohol (Mann et al., 2008).	Recommended for use in those with moderate and severe alcohol dependence after successful withdrawal, and in combination with a psychological intervention. It may also be considered for use (in combination with a psychological intervention) in harmful drinkers and those with mild dependence who either have not responded to psychological interventions alone or who have specifically requested a drug therapy (NICE, 2011).
Oral naltrexone (Revia or Vivitrol)	For use as an additional therapy within a comprehensive treatment program including psychological guidance for detoxified patients who have been opioid-dependent and for patients with alcohol dependence to support abstinence.	Abstinence	Naltrexone is an opioid receptor antagonist, working to block the opiate receptors in the brain. Blocking these receptors acts to prevent some of the positive consequences experienced after drinking alcohol, thereby decreasing the likelihood of excessive drinking (Volpicelli et al., 1994).	As above.
Disulfiram (Antabuse)	An alcohol deterrent, for the treatment of carefully selected and co-operative patients with drinking problems. Must be accompanied by appropriate supportive treatment.	Abstinence	Disulfiram works to deter drinking due to the strong adverse reactions experienced when alcohol is consumed. When mixed with alcohol it can result in unpleasant reactions including vomiting, flushing, and nausea (Skinner et al., 2014).	Recommended for use in those with moderate and severe alcohol dependence after successful withdrawal, in combination with a psychological intervention. To be used where there is a goal of abstinence but for whom acamprosate and oral naltrexone have not been suitable (NICE, 2011).
Nalmefene (Selincro)	For reduction of alcohol consumption in adult patients with alcohol dependence who have a high DRL, without physical withdrawal symptoms and who do not require immediate detoxification. Must be used in conjunction with continuous psychosocial support. Initiated only in patients who	Reduced drinking	Nalmefene is an opioid system modulator, working as an opioid receptor antagonist at the mu and sigma receptors and a partial agonist at the kappa receptor (Bart et al., 2005). It is thought that nalmefene acts to reduce the reinforcing effects of alcohol which occur after repeated heavy use (van den Brink et al., 2013).	Recommended by NICE as a possible treatment for reducing alcohol consumption, to be used in conjunction with psychosocial support (NICE, 2014a).

	continue to have a high DRL two weeks after initial assessment.			
Topiramate (Topamax)	To treat adults, adolescents and children with seizures.	Has been studied in relation to its efficacy in reducing alcohol consumption.	Topiramate is not currently licensed as a treatment for alcohol dependence. However, this anticonvulsant drug has been studied in relation to treating alcohol dependence (Guglielmo et al., 2015). It is thought to reduce cravings by acting on the glutamate system in the brain and blocking the release of dopamine (Johnson, 2005).	Topiramate is not currently recommended by NICE for moderate and severe alcohol dependence after successful withdrawal. A review of evidence on topiramate conducted for the NICE Evidence Update (NICE, 2013) has suggested that more research is needed to establish efficacy.
Baclofen (Lioresal)	Baclofen is indicated for the relief of spasticity of voluntary muscle resulting from a number of disorders including multiple sclerosis, cerebral palsy and a range of spinal problems.	Has been studied in relation to its efficacy in reducing alcohol consumption.	Baclofen is not currently licensed for alcohol treatment in the UK. However, its potential use in alcohol treatment has been studied (Bschor et al., 2018) It works on the gama-aminobutyric acid (GABA)-B receptors in the brain to produce anti-craving and anti-reward effects (Johnson, 2005).	Baclofen is not currently recommended by NICE as a treatment for moderate and severe alcohol dependence after successful withdrawal. A review of evidence on baclofen conducted for the NICE Evidence Update (NICE, Jan 2013) has not changed this position. In France it has been given a temporary licence for treating alcohol dependence but its use remains controversial due to potential harms of the drug (Naudet and Braillon, 2018).

The drugs described in Table 3 work in different ways. Whilst disulfiram acts to deter drinking, the newer drugs, such as acamprosate, naltrexone and nalmefene, act directly on the physiological processes in the brain that influence the addiction to alcohol (Fuller and Gordis, 2004). The UK NICE (2011) guideline on AUDs recommends two classes of pharmacological treatment – drugs to treat alcohol withdrawal (such as benzodiazepines), and drugs to promote abstinence or prevent relapse after withdrawal (such as acamprosate or oral naltrexone, or where these are not suitable, disulfiram). A later addition to the UK-approved drug treatments is nalmefene, to be used where the treatment goal is reduced drinking. Nalmefene was recommended in a NICE Technology Appraisal (NICE, 2014a), which places a requirement on NHS authorities in England to fund the drug, usually within three months of the guideline publication (NICE, 2018).

A key feature of pharmacological therapy for alcohol problems is that it is mainly used in combination with a psychosocial therapy. UK guidelines recommend that psychosocial interventions are used alongside all drug treatments for alcohol dependence (NICE, 2011). Earlier studies suggest that this combined approach results in better outcomes for patients and is more cost-effective (Carroll et al., 1997; Berglund, 2005). The motivational style used in psychosocial therapies is thought to create a positive relationship between the practitioner and patient, which can act to increase compliance with medication, and support a more positive outlook among patients (Raistrick et al., 2006).

Drug therapies for alcohol problems can be prescribed in a number of different settings, although the primary care setting is thought to be advantageous given that many patients do not wish to take up specialised treatment or do not have access to it. (Jonas et al., 2014). However only a small proportion of patients requiring alcohol treatment receive a pharmacotherapy for this (Mark et al., 2009; Thompson and Pirmohamed, 2016). Reasons identified in the literature include: a lack of expertise; lack of confidence in the medication; concerns about side effects; and the heterogeneous nature of alcohol problems, where no one medication works for all patients (Litten et al., 2012; Goh and Morgan, 2017).

This section briefly summarises the evidence in relation to naltrexone, acamprosate, disulfiram, topiramate and baclofen in reducing drinking or preventing a return to heavy drinking. The nalmefene evidence is discussed in detail in Chapter 3. The evidence discussed here mainly derives from systematic reviews, which are considered to be one of the best sources of evidence, due to the rigour applied in searching and appraising the literature (Hess,

2004; Ioannidis, 2016). Some of these systematic reviews include meta-analyses, which combine quantitative results from multiple trials to achieve a summary treatment effect (Ebrahim et al., 2016). Systematic reviews (some with meta-analyses) suggest that both naltrexone and acamprosate are efficacious in reducing drinking or preventing a return to heavy drinking (Rösner et al., 2010a; Maisel et al., 2013; Jonas et al., 2014; Donoghue et al., 2015), with naltrexone reported as being more effective for patients wanting to control their heavy drinking, and acamproste for those wishing to achieve abstinence (Maisel et al., 2013).

Evidence from the disulfiram trials included in the Jonas review (Jonas et al., 2014) did not adequately support any improvement in alcohol consumption outcomes, although it was added that some patients with AUDs may benefit. Supervision has been shown to be an essential ingredient in helping patients to take disulfiram and some studies (including a systematic review) have suggested that properly supervised use of this drug can achieve positive drinking outcomes (Chick et al., 1992; Skinner et al., 2014).

Although topiramate and baclofen are not currently recommended by UK guidelines (NICE, 2013), they may have potential in treating individuals with alcohol dependence. Several systematic reviews with meta-analyses conclude that topiramate is superior (to placebo or active comparators) in relation to some drinking outcomes (Arbaizar et al., 2010; Blodgett et al., 2014; Jonas et al., 2014). The evidence for baclofen is mixed. Two recent systematic reviews and meta-analyses reported it to be superior to placebo in relation to abstinence-based drinking outcomes (Pierce et al., 2018; Rose and Jones, 2018). Others, however, have concluded that there is little or no evidence for baclofen over placebo treatment (Jonas et al., 2014; Bschor et al., 2018).

In considering the evidence for pharmacological treatment for alcohol problems, it is important to take account of the limitations of trial evidence. This is emphasised in a recently published systematic review and meta-analysis (Palpacuer et al., 2017) examining the efficacy of five different pharmacological treatments (naltrexone, acamprosate, nalmefene, topiramate and baclofen) in reducing alcohol consumption in patients with alcohol dependence. It concluded that there was insufficient evidence for any of the drugs examined, and high levels of bias in the studies included. These issues are discussed further in Chapter 3 in relation to the nalmefene evidence base.

1.4 Rationale for the study

Nalmefene is controversial for a number of reasons. Firstly, it has unique features which distinguish it from other licensed drugs for treating alcohol dependence. These include that it is the first alcohol dependence drug licensed to be taken on an 'as-needed' basis, whereby patients decide for themselves when to take a tablet. The guidance is that it should be taken 1–2 hours before they think they will have alcohol (Lundbeck Ltd., 2013b; Mann et al., 2013). Another distinguishing feature is that it is the first and only drug licensed for the reduction of alcohol consumption in patients intending to continue to drink; other approved drugs are licensed for maintaining abstinence in patients who have successfully withdrawn from alcohol use (NICE, 2011; Aubin and Daeppen, 2013; Keating, 2014). Nalmefene has been described as a 'paradigm shift' in alcohol treatment because of some of these features, and its novel nature has also been highlighted in some media reports (Mann et al., 2013; Press Association, 2014; Smith, 2014).

Secondly, there are mixed views about the evidence for nalmefene in reducing alcohol consumption. On the one hand, reports from the Lundbeck-sponsored clinical trials conclude that nalmefene reduces alcohol consumption in patients with alcohol dependence, and that the drug has wider benefits in relation to its potential in engaging more patients into treatment (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014a). Others, however, have queried the reported trials' results and claimed benefits of nalmefene for treating alcohol dependence, raising issues about the conduct and reporting of the trials (Braillon, 2014; Spence, 2014; Palpacuer et al., 2015; Fitzgerald et al., 2016). Regulatory bodies in a number of countries, including Germany and Sweden, concluded that there was no evidence that nalmefene offered any additional benefit over existing treatment options (IQWIG, 2014; Stafford, 2014; Tandvårds-och Läkemedelsförmånsverket, 2015) and regulatory and advisory body decisions to approve and recommend nalmefene have been questioned (Braillon, 2014; Palpacuer et al., 2015; Fitzgerald et al., 2016).

Thirdly, nalmefene was expected to be prescribed mainly in primary care (Lundbeck Ltd., 2012; Scottish Medicines Consortium, 2013; NICE, 2014b) and there are suggestions that it was heavily marketed towards this setting (Spence, 2014; Fitzgerald et al., 2016). However, concerns were expressed that GPs could experience challenges in identifying patients who were suitable for nalmefene treatment and to support them whilst taking nalmefene (Kerr, 2013; Scottish Medicines Consortium, 2013; Drug and Therapeutics Bulletin, 2014). The

licensing conditions for nalmefene require that it be prescribed to a very specific sub-group of drinkers: those with a diagnosis of alcohol dependence, but without withdrawal symptoms, and who are drinking at a 'high drinking risk level'[5] (at both an initial assessment and 2 weeks later). They also require that patients are given continuous psychosocial support alongside their nalmefene treatment (Lundbeck Ltd., 2013b).

It is these uncertainties about the potential advantages and disadvantages of nalmefene and how it is implemented in primary care that have highlighted the need to understand its use in UK primary care and what factors might have influenced this. The results of this study will have wider implications for other alcohol treatment and policy, in particular, interventions which may be targeted towards primary care.

1.5 Study aim and research questions

The overall aim of this thesis is to describe and understand patterns and influences in nalmefene prescribing in UK primary care. To achieve this, four key study research questions will be addressed:

1. To what extent and how has nalmefene been prescribed in UK primary care?
2. How has nalmefene been marketed and what influence has this had on the way in which the drug is perceived and used in the UK?
3. What (other) factors have influenced nalmefene prescribing in UK primary care?
4. What are the perspectives of key stakeholders in the alcohol field regarding nalmefene, its promotion and its use in UK primary care?

1.6 Structure of the thesis

The thesis comprises eight chapters, including this introductory chapter.

Chapter 2 draws on the literature on pharmaceutical marketing, outlining the approaches used by companies to promote their products, the risks associated with these, and how

[5] Defined as alcohol consumption of 60g or more per day for men, and 40g or more per day for women (WHO, 2000).

pharmaceutical marketing is regulated. This chapter sets the scene for Chapter 6, which explores and describes nalmefene marketing activities.

Chapter 3 summarises the evidence for nalmefene in reducing alcohol consumption in patients with alcohol dependence, drawing on published scientific literature identified using a systematic literature search following PRISMA guidelines. It also outlines key criticisms raised regarding the nalmefene evidence, drawing on wider literature including guidelines on the conduct and reporting of clinical trials.

Chapter 4 describes the methodology adopted for the study. It discusses the mixed-methods approach to conducting research and how this has been used to study nalmefene use in UK primary care.

Chapter 5 presents an analysis of UK primary care data on nalmefene prescribing in order to understand national trends and how the drug has been used in individual patients. It outlines how nalmefene has been used in real-world clinical practice. Some prescribing patterns from this chapter are further explored via the qualitative study (Chapter 7).

Chapter 6 describes the marketing activites undertaken for nalmefene and discusses their potential role in how the drug was subsequently used and adopted in practice. It is based on a documentary analysis of the scientific and grey literature and complements qualitative data on participant experiences of nalmefene marketing activities described in Chapter 7.

Chapter 7 presents qualitative perspectives on nalmefene obtained from interviews with a range of professionals in the alcohol field. These provide additional insights into some of the the earlier findings relating to the evidence for nalmefene (Chapter 3), how it has been used in primary care (Chapter 5), and how it has been marketed (Chapter 6).

Chapter 8 summarises and discusses the key qualitative and quantitative findings from across all study strands, synthesising them to gain a more comprehensive account of nalmefene prescribing patterns and influences. The findings are discussed in relation to the wider literature, and implications for alcohol treatment and policy are presented. The strengths and limitations of the study and my reflections on the research process are also discussed, followed by the overall study conclusion.

2 PHARMACEUTICAL MARKETING AND CONFLICTS OF INTEREST

2.1 Introduction

One of the aims of this study is to understand what factors have influenced nalmefene prescribing in UK primary care. The evidence for nalmefene is discussed in Chapter 3. Another potential influencing factor explored in this study is pharmaceutical marketing. This chapter provides a brief introduction to pharmaceutical marketing which is then further explored in Chapter 6 relating to the marketing activities undertaken for nalmefene. This chapter covers different forms of pharmaceutical marketing, the risks associated with these, and approaches used to regulate marketing activities. It also includes a brief discussion of conflicts of interest, a topic explored in Chapter 6 in relation to nalmefene.

2.2 What is pharmaceutical marketing?

Marketing or promotional activities are integral to the business of pharmaceutical companies, who use a variety of well-recognised and established approaches to promote their products. All companies do this within the limits imposed by their governments for the promotion of medicines. The WHO defines pharmaceutical promotion as "*all informational and persuasive activities by manufacturers and distributers, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs*" (WHO, 1988, p. 2). Although methods to increase the uptake of pharmaceutical products have traditionally focused on individual consumers, marketing approaches have expanded to account for the social and political context of prescribing, now engaging a wide variety of stakeholders – groups, networks and individuals with influence over prescribing decisions (Pesse et al., 2006).

2.3 What forms of marketing are used by the pharmaceutical industry?

Activities to promote pharmaceutical products are many and varied. Whilst some seek to influence prescribers and healthcare professionals, others are targeted towards the public or patients, patient groups, or other networks or groups.

2.3.1 Marketing to prescribers or healthcare professionals

Conveying information about a drug to prescribers and healthcare professionals is a key aspect of pharmaceutical marketing (Badcott and Sahm, 2013). Industry-sponsored materials can be distributed in a variety of ways, including mail-outs, via drug representatives, via

medical journals, and via conferences and educational events (House of Commons Health Committee, 2005; Goldacre, 2013). Many doctors have cited information from drug representatives as a main source of prompt information about medicines (Prosser et al., 2003). Previous research suggests that doctors who interact with drug representatives are more likely to prescribe branded products (Spurling et al., 2010; Fickweiler et al., 2017), although doctors have tended to say that their own prescribing behaviour is not influenced by such visits (Rutledge et al., 2003; Morgan, 2006; Lieb and Scheurich, 2014).

Medical journals, a key source of information for health care professionals, have been described as an important marketing tool for pharmaceutical companies (Moffatt and Elliott, 2007; Spielmans, 2015). Companies pay journals to publish adverts for their products and to order 'reprints' of individual papers so that these can be distributed more widely (Smith, 2005; Goldacre, 2013, p. 247). Journals also publish results from clinical trials and from systematic reviews and meta-analyses, many of which are sponsored by pharmaceutical companies (Dunn and Coiera, 2014; Ebrahim et al., 2016; Ioannidis, 2016). A majority of meta-analyses on anti-depressants for depression published between 2007 and 2014 were either authored by pharmaceutical company employees or individuals with links to the company (Ebrahim et al., 2016). Some trials papers are written by professional medical writers employed by the pharmaceutical company (Spielmans, 2015; Matheson, 2016), a detail which is sometimes not made explicit in published papers (Goldacre, 2013 p. 289; Matheson, 2016). Rather, in an effort to present these as independent of pharmaceutical company involvement, these papers can appear under the authorship of an academic, physician, or someone considered to be a 'key opinion leader' (KOL), a practice referred to as 'ghost-writing' (Moffatt and Elliott, 2007).

Healthcare professionals are required to maintain their skills and knowledge, and one way of doing this is through attending conferences and continuing medical education events (Stamatakis et al., 2013). These events provide another route for pharmaceutical companies to raise awareness of their products. The costs of a large proportion of medical training and conferences are met by the pharmaceutical industry (House of Commons Health Committee, 2005; Avorn and Choudhry, 2010) and this may create opportunities to influence the content of these events (Rutledge et al., 2003; Avorn and Choudhry, 2010; Stamatakis et al., 2013). Pharmaceutical companies may further benefit by using KOLs to relay information about

their products (Burton and Rowell, 2003; Moynihan, 2008). As with journal papers, using KOLs can enhance the credibility of the message being relayed (Burton and Rowell, 2003).

2.3.2 Marketing to patients or the public

Pharmaceutical marketing also targets patients and the public. Direct-to-consumer marketing of pharmaceuticals, whilst prohibited in the UK, is permitted in the USA, for example, with advertisements for drugs appearing on TV and other media (Schwartz and Woloshin, 2019). Aside from raising awareness of a product, this type of marketing also seeks to raise awareness of diseases and conditions, emphasising their biological foundations and encouraging individuals to talk to their doctors about possible medical treatments for these (Edgar, 2013; Adams and Harder, 2018). Numerous examples of this type of approach – referred to as 'disease-mongering' – exist, from irritable bowel syndrome and high cholesterol (Moynihan and Henry, 2006) to social anxiety disorder (Tiefer, 2006) and pre-menstrual dysphoric disorder (Ebeling, 2011).

2.3.3 Stakeholder marketing

Pharmaceutical companies engage with a wide range of other individuals or groups who have influence in the prescribing environment, including governments, formulary committees, regulators, pharmacists, health care managers and patient groups (Pesse et al., 2006). This type of activity, described as 'stakeholder marketing', can help corporations form relationships that may be beneficial to them or their products (Hastings and de Andrade, 2016). For example, pharmaceutical companies have provided funding to local healthcare commissioning bodies in the UK for projects and events relating to their products, some of which has not been fully declared (Moberly, 2018); they have also funded the work of many patient groups and charities (Burton and Rowell, 2003; Batt, 2005; Schwartz and Woloshin, 2019). Edgar (2013) describes these organisations as 'crucial mediators' in influencing local and national policy positions as well as clinical practice (Edgar, 2013). Patients groups also have an important role in regulatory decisions on new drugs; they act as consultees in regulatory assessments of new drugs, many of them having already received funding from a pharmaceutical company (Mandeville et al., 2019). KOLs recruited by pharmaceutical companies may also be considered as influential stakeholders in relation to pharmaceutical marketing, as they have a voice in a number of arenas, including research, publications, conferences, education, the media, local formulary committees and national guideline committees (Moynihan, 2008; Austin and Halvorson, 2019). The benefits for pharmaceutical

companies may be lucrative, with studies showing that the prescribing of drugs increases among those who have attended presentations by KOLs compared with those who have not (Alves et al., 2019).

2.4 Risks associated with pharmaceutical marketing

The pharmaceutical industry invests heavily in promotional activities, an amount which may in some instances exceed expenditure on research and development (Gagnon and Lexchin, 2008). This increasing level of marketing activity and the methods used have been criticised, with concerns raised about the increasing influence of the industry and the potential harms associated with this (House of Commons Health Committee, 2005; Goldacre, 2013; Gotzsche, 2013).

Pharmaceutical industry involvement in the scientific literature can potentially bias the information available to clinicians. For example, pharma-sponsored publications have tended to present favourable results for the sponsor's drug (Als-Nielsen et al., 2003; Lexchin et al., 2003; Smith, 2005), drawing on specific design and reporting approaches to present findings in the best possible light, whilst studies showing less favourable results remain unpublished (Moffatt and Elliott, 2007). This can result in an overly optimistic evidence base, which can go on to influence guidelines and prescribing, and with negative consequences for patients in some cases (Goldacre, 2013, p. 247; Spielmans, 2015). The over-promotion of expensive drugs offering minimal benefit has implications for health care resources, which may be diverted away from other potentially useful and cheaper treatments (Spurling et al., 2010). The dangers of drugs which have been over-promoted without fully disclosing their health risks have been highlighted, for example, in relation to Oxycontin (Van Zee, 2009) and Vioxx (Krumholz et al., 2007). Under-reporting of side effects has also been identified in ghost-written papers (Sismondo, 2007).

Marketing activities aimed at the public can also be potentially harmful. Few direct-to-consumer drug advertisements include information about non-drug options for a condition and many have tended to minimise the risks of taking the drug (Kim, 2015; Schwartz and Woloshin, 2019). Harms to patients may also occur where the marketing seeks to encourage the uptake of medical treatments for conditions that could be viewed as part of the normal spectrum of human behaviour or could be addressed by non-pharmacological approaches (Edgar, 2013). A US study reported that some conditions (dry eye disease, low testosterone)

not considered to be conventional diseases were among the main issues covered in disease awareness campaigns, risking over-diagnosis, over-treatment and unnecessary expense (Schwartz and Woloshin, 2019). Vulnerable people and those with poor health literacy may be particularly susceptible to direct-to-consumer promotion (Carter et al., 2010), as described by Edgar (2013, p. 301), who writes that patient vulnerability can make them "*susceptible to any exaggerated promises made on behalf of new therapies, and with a tendency to read more into claims made on behalf of therapies than is warranted.*"

A wider risk of these marketing activities is that agendas, debates, policies and educational content may be more commercially-driven, rather than reflect a balance of views or approaches (Goldacre, 2013; Batt, 2014; Ozieranski et al., 2019). It may leave organisations, agendas, interventions and policies that run counter to pharmaceutical industry interests, and are therefore unsupported financially, without a voice (Edgar, 2013).

2.5 Regulation of pharmaceutical marketing

Pharmaceutical marketing regulations vary widely across countries, including in the extent to which governments get involved in limiting or monitoring marketing activities (Alves et al., 2019). For example, whilst governments in many countries have banned direct-to-consumer advertising due to concerns about potential harms to patients, this is still allowed in the US and New Zealand (although there are calls for it to be banned there too) (Every-Palmer and Howick, 2014; McCarthy, 2015; Bulik, 2017; Schwartz and Woloshin, 2019). Many countries rely on the industry to self-regulate promotion (Lexchin, 2012), including in the UK, where self-regulation is through the Association of the British Pharmaceutical Industry (ABPI) code of practice (Association of the British Pharmaceutical Industry, 2019).

Self-regulation policies have been criticised for failing to adequately protect public health, for including vague definitions of promotion and for failing to encapsulate harm prevention (Lexchin, 2012; Alves et al., 2019). Regulatory control policies more generally may be unable to fully account for newer forms of promotional activities now undertaken by pharmaceutical companies (Parker et al., 2018) and be also be hampered by the global availability of online information (making it harder to uphold the regulations imposed in a single country) (De Freitas et al., 2014) and the interdependencies between individuals, institutions and regulatory bodies which may make some regulatory decisions more complex (Alves et al., 2019).

2.6 Conflicts of interest

Pharmaceutical industry funding of organisations or individuals associated with health care is common (Fontanarosa and Bauchner, 2017; Feldman et al., 2018). Whilst the resulting collaborations can be beneficial to medicine (Rosenbaum, 2015), they can also present a potential conflict of interest (COI). The International Committee of Medical Journal Editors (ICMJE) defines a COI as follows:

> *The potential for conflict of interest and bias exists when professional judgement concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain). Perceptions of conflict of interest are as important as actual conflicts of interest.* (ICMJE, 2019, p. 3)

Those relating to the pharmaceutical industry are common, given the extent of industry involvement in funding health care research (including clinical trials) (Dunn and Coiera, 2014), and the relationships which have been formed between individuals in industry and those working in the health care and research sector (Fontanarosa and Bauchner, 2017).

Having a COI does not necessarily imply that judgements are influenced unduly by the financial relationship or that there is any misconduct (Lee, 2008). However, research on COIs suggests there is a positive association between scientific papers concluding in favour of a drug and the presence of author COIs relating to the drug company (Wang et al., 2010; Dunn et al., 2016; Ioannidis, 2016). The receipt of gifts from pharmaceutical companies can also create a reciprocal obligation in physicians (Katz et al., 2003). These studies highlight the importance of declaring COIs in journal papers or other forums so that others can decide for themselves whether there is any resulting bias from the COI (Goldacre, 2013, p. 330).

As with regulations on promotion, policies relating to the disclosure of pharmaceutical industry funding differ across countries. In the USA there is legislation requiring mandatory disclosure of pharmaceutical industry payments to health care professionals and patient organisations (Alves et al., 2019). In Europe, policies vary, with some countries adopting a similar policy to the USA and others relying on industry self-regulation (Fabbri et al., 2018a; Alves et al., 2019). In the UK, disclosure of funding is voluntary and individuals who have received pharmaceutical funding can decide not to fully disclose these details (Fabbri et al., 2018a; Feldman et al., 2018). COIs for health service employees are inadequately recorded

by UK NHS Trusts (Feldman et al., 2018). These gaps have led to calls for stronger disclosure policies in the UK, including a central register for financial payments similar to that adopted by the USA (Kmietowicz, 2016; Feldman et al., 2018) and a strengthening of disclosure policies for organisations that contribute to policy or regulatory processes as well as communications to the media (Rothman et al., 2011; Mandeville et al., 2019).

Whilst there have been efforts to strengthen and standardise disclosure policies in scientific journals (ICMJE, 2019), the current system of disclosure for researchers is viewed as insufficient in allowing readers to fully assess potential bias (Grundy et al., 2020). COIs in scientific papers are still under-reported, incomplete, inconsistently declared and inaccessible (Dunn et al., 2016; Shawwa et al., 2016; Grundy et al., 2020).

2.7 Summary

Pharmaceutical companies use a variety of approaches to promote their products. While efforts to influence uptake of their products have traditionally focused on direct engagement with prescribers or other healthcare professionals as well as the public in some countries, newer forms of promotional activity have sought to engage with a wide range of stakeholders who may have some influence over prescribing decisions. The increased level and influence of pharmaceutical marketing activity creates opportunities for bias in the healthcare system and may also incur harms to health. Efforts to regulate marketing activities, and policies to promote transparency in relationships may not adequately protect the health care system from any potential bias. The marketing activities undertaken for nalmefene will be discussed in Chapter 6 of this thesis.

3 A SYSTEMATIC CRITICAL NARRATIVE REVIEW OF THE EVIDENCE FOR NALMEFENE IN REDUCING ALCOHOL CONSUMPTION

3.1 Introduction

Nalmefene is considered to be controversial, as mentioned in Chapter 1 (Section 1.4) of this thesis. Part of the controversy relates to the randomised controlled trial (RCT) evidence for nalmefene, which has been met with mixed reviews. This chapter summarises the evidence for nalmefene in reducing alcohol consumption in patients with alcohol dependence. It uses papers identified in an updated systematic literature search, drawing on the original trials papers, secondary analyses of the trial data, and systematic reviews and meta-analyses which include nalmefene. Unpublished studies of nalmefene identified in clinical trials registers are also described. This is followed by a discussion of the nalmefene evidence, drawing on issues raised in critical papers about the clinical trials and the literature on good clinical trials practice.

3.2 Nalmefene literature search methods

Systematic searches for published and unpublished studies were made for the period up to September 2017. For the period up to December 2014, searches for studies relating to nalmefene for alcohol treatment had been undertaken for an earlier review (Fitzgerald et al., 2016); a further identical search was conducted for the period December 2014 to September 2017 using the same search strategy. The following databases were searched: PubMed, Cinahl via EBSCOHost, HealthSource via EBSCOHost, Web of Science Core Collection, and Google Scholar (UK). Searches were also made in relevant clinical trials registers. Full details of the search strategy are in Appendix 1.

A full list of published papers from both searches was obtained. After the removal of duplicate records (including records from the 2014 search which re-appeared in the 2017 search), the titles and abstracts of papers were screened. Records were excluded at this stage if they were off-topic (not relating to nalmefene for alcohol treatment in humans); conference abstracts; news items, letters or commentaries; or where the full text was not available in English. The full text for the remaining papers was checked to identify those required for the nalmefene evidence review (original trials of nalmefene for reducing alcohol consumption; secondary analyses of the nalmefene trials; and systematic reviews or meta-analyses of the nalmefene trial data). The remaining papers (narrative reviews, other studies of nalmefene)

were excluded for the evidence review but would inform the documentary analysis of nalmefene marketing in Chapter 6.

3.3 Results of the nalmefene literature search

Figure 1 provides a PRISMA flowchart to illustrate the study inclusions and exclusions (Moher et al., 2009) and details relating to the rationale for exclusion. Thirty papers were identified for inclusion in the evidence review – seven original clinical trials papers; eleven secondary analysis papers; and twelve systematic review and/or meta-analysis papers. The evidence on nalmefene from these papers is discussed in the following sections. An additional eleven studies identified through the clinical trials databases are summarised in Table 8 (Section 3.3.5, p. 72).

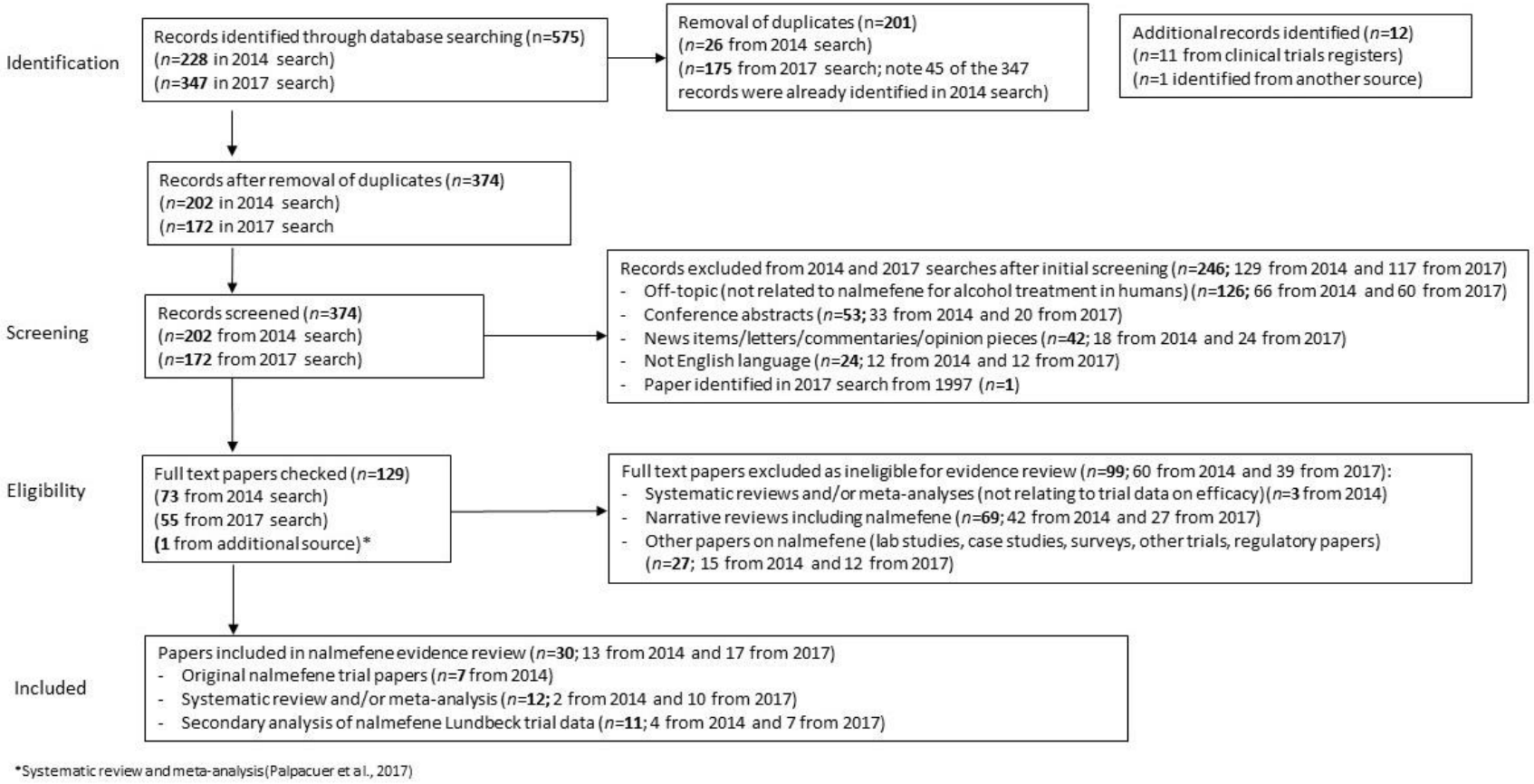


Figure 1: PRISMA diagram for 2014 and 2017 searches combined

3.3.1 Evidence from the early clinical trials of nalmefene

Four clinical studies of nalmefene in patients with alcohol dependence were undertaken prior to Lundbeck taking on the licensing of nalmefene; three were conducted in the USA, and one in Finland (Table 4). The first, a small single-site pilot study reported that nalmefene can be given safely and may reduce alcohol consumption (Mason et al., 1994). A later single-site study (Mason et al., 1999) reported that patients who were given nalmefene combined with CBT were less likely to relapse to heavy drinking compared with a placebo group (no significant difference between nalmefene and the placebo was found for the other 2 study outcomes).

The other two trials were larger and based on multiple sites but arrived at different conclusions about nalmefene efficacy. The US study (Anton et al., 2004) reported no significant difference between nalmefene and the placebo in the number of monthly heavy drinking days (HDDs)(see Abreviations and definitions), whilst the Finnish study (Karhuvaara et al., 2007) reported a significantly greater decrease in average monthly HDDs among patients prescribed nalmefene compared with those given the placebo. These two trials differed methodologically, including in their sample size (with a larger sample in the Finnish study); length of study (longer in the Finnish study); dosage (nalmefene was given daily in the US study and 'as-needed' in the Finnish study); and in the type of psychosocial support package given to patients (MET was used in the US study, whilst elements of the BRENDA package (Starosta et al., 2006) were use in the Finnish study). The US study authors suggested that the non-significant effects for nalmefene may be related to two factors: that the psychosocial therapy used was of lower intensity compared with that used in previous studies, resulting in lower treatment compliance; and that the sample size may have been too small to detect a statistically significant result for nalmefene.

Table 4: Early nalmefene trials

Study	Population, recruitment and setting	Treatment and control group	Primary outcome measures	Results	Funding source
(Mason et al., 1994)	Pilot study of 21 patients with alcohol dependence in a single site in USA	12 weeks' treatment with 10mg/40mg nalmefene or placebo	Rate of relapse to heavy drinking; % days abstinent; standard drinks per drinking day; measured over 12 weeks	The 40 mg group had a significantly lower rate of relapse (p=0.05), and a greater increase in the number of abstinent days/week (p=0.09), than the other treatment groups. A significant decrease in the number of drinks/drinking day for both nalmefene groups (p=0.04), but not for placebo	Funded by National Institute on Alcohol Abuse and Alcoholism (NIAAA).
(Mason et al., 1999)	105 adults with alcohol dependence (outpatients recruited through advertisements and press releases) in a single site in USA (Florida) in an alcohol disorders research clinic	12 weeks' twice-daily treatment with10mg/40mg nalmefene or placebo; all patients received weekly CBT sessions over 12 weeks	As for Mason et al., 1994	Effect on 1 of 3 outcomes: fewer nalmefene patients (37%) relapsed to heavy drinking compared with placebo (58.8%) (p=0.02)	Funded by NIAAA; drug and placebo provided by IVAX Corp.
(Anton et al., 2004)	270 adults with alcohol dependence, recruited through clinical referrals and advertisements in 13 sites in USA (11 States), mainly university medical/research centres	12 weeks of daily 5mg/20mg/40mg nalmefene or placebo; all patients given 4 sessions of MET.	HDDs per month	No statistically significant difference between groups	Funded by Biotie (including statistician and preparation of manuscript)
(Karhuvaara et al., 2007)	403 adults with difficulty controlling drinking with at least 18 HDDs and no more than 14 consecutive abstinent days during the previous 12 weeks, recruited mainly through news advertisements. 15 sites across Finland (5 specialist treatment; 6 private GP practices; 2 occupational health-care offices; and 2 clinical research sites)	28 weeks of 20mg nalmefene or placebo, taken as needed; after 2 weeks, the dose could be doubled or halved if necessary; all patients given some elements of BRENDA psychosocial support.	HDDs per month	The nalmefene group had fewer HDDs during the 28 weeks of treatment than the placebo group (final month 8.8 versus 10.6, p=0.0065)	Funded by Biotie; sponsor involved at all stages.

Note: Adapted from Table 1 in (Fitzgerald et al., 2016)

3.3.2 Evidence from the Lundbeck-sponsored clinical trials of nalmefene (for pre-marketing authorisation)

Three Lundbeck-funded studies – ESENSE 1 (Mann et al., 2013), ESENSE 2 (Gual et al., 2013), and SENSE (van den Brink et al., 2014a) – were conducted between 2008 and 2011 in 19 countries (using 149 sites) across Europe (Fitzgerald et al., 2016). These trials formed the basis of the clinical evidence used by the European Medicines Agency (EMA) to assess nalmefene, and thereafter by the UK National Institute for Health and Care Excellence (NICE) appraisal committee. They compare the efficacy of 'as-needed' nalmefene 18mg/day (plus psychosocial support using BRENDA) to a placebo (plus psychosocial support using BRENDA) in reducing the number of HDDs and total alcohol consumed (TAC).

They report results for two sets of patients – the total trial population and a sub-group of patients with a high drinking risk level (DRL) at both the screening and randomisation stage (two weeks later). A high DRL is defined as alcohol consumption of 60g or more per day for men and 40g or more per day for women, according to the risk levels defined by the WHO. The reported results for the total trial population indicate a significant effect of nalmefene over placebo treatment for some, but not all, of the trial outcomes: in reducing HDDs (at 6 months in ESENSE 1 and 2, and 12 months in SENSE) and in reducing TAC (at 6 months in ESENSE 1, and 12 months in SENSE). The results reported for the sub-group patients generally show relatively larger effect sizes for nalmefene over the placebo in decreasing HDDs and TAC across the three trials. In these three trials the BRENDA sessions were delivered at weekly intervals for the first two weeks and monthly sessions thereafter (the initial session lasting 30–40 minutes and subsequent sessions 15–30 minutes). Details of the trials are presented in Table 5 (as summarised in Fitzgerald et al., 2016). It is notable that, in the ESENSE 1 and 2 trials (Gual et al., 2013; Mann et al., 2013) and a subsequent pooled sub-group analysis of the RCT efficacy data (van den Brink et al., 2013), nalmefene was no better than the placebo over the whole treatment period in the group of patients who did reduce their consumption in the two weeks between initial assessment and randomisation.

Table 5: Lundbeck-sponsored nalmefene trials

Study	Population, recruitment and setting	Treatment and control group	Study primary outcome measures	Results	Funding source
ESENSE 1 (Mann et al., 2013)	604 adults with alcohol dependence (DSM-IV-TR). Recruited in 39 sites in Austria, Finland, Sweden and Germany, via in- and out-patient settings including advert-isements.	24 weeks of nalmefene 18mg (as-needed) plus psychosocial support (BRENDA) v 24 weeks of placebo plus psychosocial support (BRENDA)	Change from baseline to month 6 in the number of HDDs /month and TAC (grams/day)	Nalmefene patients had 2.3 fewer HDDs/month compared with placebo patients [95% CI: -3.8 to -0.8; *p*=0.002] and consumed 11.0g less alcohol per day compared with the placebo group [95% CI: -16.8 to -5.1; *p*=0.003]. Note: the results of a sub-group analysis of ESENSE 1 patients drinking at a high DRL at both screening and randomisation were reported in van den Brink et al. (2013): this paper reported that nalmefene patients had 3.7 fewer HDDs/month [95% CI: -5.9 to -1.5; *p*=0.001] and 18.3g less alcohol per day [95% CI: -26.9 to -9.7; *p*<0.0001].	Lundbeck sponsored the trials, was involved in the study design, data collection, analysis and interpretation, and provided medical writing assistance
ESENSE 2 (Gual et al., 2013)	718 adults with alcohol dependence (DSM-IV-TR). Recruited in 57 sites in Belgium, Czech Republic, France, Italy, Poland, Portugal and Spain, via in and out-patient clinics, advert-isements, the study site's patient pool and by spontaneous referrals.	As for ESENSE 1	As for ESENSE 1	Nalmefene patients had 1.7 fewer HDDs/month compared with placebo patients [95%CI: -3.1 to -0.4; *p*=0.012]. Although the nalmefene group consumed 5g less alcohol per day than the placebo group, this was not statistically significant [95% CI: -10.6 to 0.7 (*p*=0.088)]. Sub-group results for patients with a high DRL at both screening and randomisation were reported: nalmefene patients had 2 fewer HDDs/month than placebo [95% CI: -3.6 to -0.4; *p*=0.012] and consumed 7g less alcohol per day than the placebo group [95% CI: -13.6 to -0.4 to *p*<0.037].	As for ESENSE 1
SENSE (van den Brink et al., 2014a)	675 adults with alcohol dependence (DSM-IV-TR). Recruited in 60 sites from Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland,	52 weeks of nalmefene 18mg (as-needed) plus psychosocial support (BRENDA) v 52 weeks of placebo plus psychosocial support (BRENDA)	At trial registration, the primary outcomes were based on safety measures only. These were amended post-registration to include consumption measures. The revised primary outcomes are:	Findings reported are based on the same two co-primary outcomes as ESENSE 1 and 2 studies: No effect of nalmefene was found for either alcohol consumption variable at 6 months. At 12 months the nalmefene group had 1.6 fewer HDDs/month [95% CI: -2.9 to -0.3; *p*=0.017] and 6.5g less alcohol consumption per day in the last month [95% CI: -12.5 to -0.4; *p*=0.036].	As for ESENSE 1 and 2

	Russia, Slovakia, Ukraine and the UK, via out-patient clinics and some advert-isements.		number of patients with adverse events; % of patients withdrawing due to intolerance to treatment; change from baseline in HDDs/month; change from baseline in TAC (grams/day).	Sub-group results for patients with a high DRL at both screening and randomisation were reported. At 6 months nalmefene patients consumed 15.3g less per day in the last month compared with placebo [95% CI: -29.1 to -1.5; *p*=0.031]; no significant effect was found for number of HDDs/ month. At month 13 nalmefene patients had 3.6 fewer HDDs/month than the placebo group [95% CI: -6.5 to -0.7; *p*=0.016] and consumed 17.3g less alcohol per day in the last month [95% CI: -30.9 to -3.8; *p*=0.013].	

Note: Adapted from Table 1 in Fitzgerald et al. (2016)

3.3.3 Evidence from secondary analyses of data from the Lundbeck-sponsored nalmefene clinical trials

Eleven secondary analysis studies were identified, based on data from ESENSE 1, ESENSE 2 and SENSE. All were funded by Lundbeck, and all but one (Sinclair et al., 2014) use data from the sub-group of nalmefene trial patients (Table 6). They all report positively in relation to nalmefene – that it is superior to placebo in reducing alcohol consumption (van den Brink et al., 2013); that it is superior to placebo on certain clinical measures (including alcohol consumption, Clinical Global Impression-S (Severity of Illness), Clinical Global Impression-I (Improvement scale) and the Short Form Health Survey version 2 (SF-36) mental component summary) (Aubin et al., 2015; François et al., 2015); that it results in a greater reduction of the estimated mortality risk in patients compared with the placebo (Roerecke et al., 2015); that it is well-tolerated with no serious safety issues (van den Brink et al., 2015); and that most patients can adhere to an 'as-needed' regimen (Sinclair et al., 2014). The other studies use statistical modelling techniques and report that treatment with nalmefene plus psychosocial support was more cost-effective compared with placebo alone (Laramée et al., 2014; Brodtkorb et al., 2016; Laramée et al., 2016a) and that reducing alcohol consumption with nalmefene is clinically relevant (François et al., 2014; Laramée et al., 2016b).

Table 6: Studies based on secondary analysis of data from the Lundbeck-sponsored nalmefene trials

Study	Aims	Methods	Main findings	Funding source and COIs declared
(van den Brink et al., 2013)	To evaluate the efficacy and safety of as-needed nalmefene versus placebo in reducing alcohol consumption in a sub-group of patients who continued to drink at a high DRL after an initial assessment	Analysis of pooled sub-group[1] data from ESENSE 1 and 2 trials	Nalmefene reported as superior to placebo in reducing the number of HDDs (3.2 fewer days) [95% CI: -4.8 to -1.6; $p<0.0001$] and TAC (14.3 fewer g/day) [95% CI: -20.8 to -7.8; $p<0.001$] at 6 months (sub-group patients).	Study supported by Lundbeck (including publication charges). Lundbeck was involved in study design, data collection, analysis and interpretation (but not in the decision to submit the manuscript for publication). 6 authors: 2 Lundbeck employees; 4 with Lundbeck COIs (consultancy, research grants, honoraria, speakers fees, travel)
(Sinclair et al., 2014)	To explore whether an 'as-needed' regimen is an acceptable and feasible strategy in patients seeking help for alcohol dependence.	Analysis of pooled all-patient treated data from ESENSE 1 and 2 trials	68% of patients adhered to the 'as-needed' regimen on at least 80% of the study days. Concludes that this medication regimen would be acceptable to patients.	Study funded by Lundbeck (including for preparation of the paper). A medical communications company is acknowledged for preparing, revising and editing the paper. 6 authors: 1 Lundbeck employee; no COI statement included in paper although one of the authors was a a Lundbeck-sponsored nalmefene RCT trial author
(Aubin et al., 2015)	To evaluate the clinical relevance of nalmefene in reducing alcohol consumption in patients with high or very high DRLs.	Anaysis of pooled sub-group[1] data from the ESENSE 1 and 2 trials	Nalmefene (sub-group) patients more likely than placebo to have better outcomes on a number of measures including alcohol consumption, and scores on Clinical Global Impression, Short-Form Health Survey and Drinker Inventory of Consequences.	Study funded by Lundbeck 7 authors: 3 Lundbeck employees; 4 with Lundbeck COIs (advisory/board roles, consultancy, honoraria, speakers fees, travel)
(François et al., 2014)	To estimate the clinical relevance of reducing alcohol consumption in alcohol dependence	A model to estimate alcohol-attributable diseases and injuries in patients with alcohol dependence and to explore the clinical relevance of reducing alcohol consumption. Used statistical equations based on	In-patient episodes for alcohol-related disease and injury increased with the number of HDDs and TAC/year. Model predicted that reducing the number of HDDs by 20/year would result in a reduction of 941	Study funded by Lundbeck 9 authors: 5 Lundbeck employees; 2 employees of Creativ-Ceutical (contracted by Lundbeck to support the study); 1 author who had received an honorarium from Lundbeck for his participantion in the study

		pooled sub-group[1] data on alcohol consumption from the ESENSE 1, 2 and SENSE trials	alcohol-attributable events per 100,000 patients. A reduction in 3,000g of alcohol per year was predicted to result in 1,325 fewer events per 100,000 patients.	
(François et al., 2015)	To investigate the effect of as-needed nalmefene on health-related quality of life (HRQoL) in patients with alcohol dependence, and to relate changes in drinking behaviour to HRQoL outcomes	Anaysis of pooled sub-group[1] data from ESENSE 1 and 2 trials. Data from the Medical Outcomes Study (MOS) 36-item Short-Form Health Survey (SF-36), European Quality of life-5 Dimensions (EQ-5D) and the Drinker Inventory of Consequences (DrInC-2R) were analysed.	Compared with placebo, nalmefene sub-group patients were more likely to show improvements in HRQoL measures scores at week 24. Changes in scores were significantly associated with reductions in HDDs and TAC.	Study funded by Lundbeck, including funding for editorial support. 6 authors: 4 Lundbeck employees; 2 with Lundbeck COIs (honoraria or travel grants)
(van den Brink et al., 2015)	To evaluate the safety and tolerability of nalmefene for reducing alcohol consumption in patients with alcohol dependence	Analysis of the pooled data and pooled sub-group[1] data from the ESENSE 1, 2 and SENSE trials	Compared with placebo, nalmefene patients had a higher incidence of adverse events (75% versus 63%) and were more likely to drop-out due to adverse events (13% versus 6%). Similar results were found for the sub-group patients. The paper concludes that the drug is well-tolerated and that there are no serious safety issues.	Study funded by Lundbeck, who were involved in study design and data analysis. 6 authors: 2 Lundbeck employees; 4 with Lundbeck COIs (consultancy, research grants, honoraria, speakers fees, travel and accommodation)
(Roerecke et al., 2015)	To calculate the reduction in all-cause mortality risk resulting from nalmefene treatment in patients with alcohol dependence	Analysis of the pooled sub-group[1] data from the ESENSE 1, 2 and SENSE trials. Use of mortality risk data from meta-analyses on all-cause mortality risk	Based on sub-group data, the reduction of drinking in the nalmefene patients was associated with a greater reduction in estimated mortality risk (8%) compared with placebo [95% CI: 2% to 13%]	Study funded by Lundbeck 5 authors: 3 Lundbeck employees; 1 author with Lundbeck COIs (research funded, lead author declared there were no potential COIs

(Laramée et al., 2014)	To determine whether nalmefene plus psychosocial support is cost-effective compared with psychosocial support alone for reducing alcohol consumption in alcohol-dependent patients with high/very high DRLs, and to evaluate the public health benefit of reducing harmful alcohol-attributable diseases, injuries and deaths	Modelling study based on an analysis of pooled sub-group[1] data from the ESENSE 1, 2 and SENSE trials.	Based on sub-group data, nalmefene plus psychosocial support is reported as cost-effective (leading to avoidance of 7179 alcohol-attributable diseases/injuries and 309 deaths per 100,000 compared with psychosocial support alone over 5 years). Concludes nalmefene is cost-effective with public health benefits	Study funded by Lundbeck. 9 authors: 3 Lundbeck employees; 3 employees of RTI Health Solutions (contracted by Lundbeck to support the study); and 3 with Lundbeck COIs (honoraria for participating in the study)
(Brodtkorb et al., 2016)	To evaluate costs and health outcomes of nalmefene plus psychosocial support, compared with psychosocial support alone, for reducing alcohol consumption in alcohol-dependent patients (with a specific focus on societal costs associated with productivity losses and crime)	A modelling study of costs and health outcomes of nalmefene treatment over 5 years, using the nalmefene sub-group[1] data from the ESENSE 1, 2, and SENSE trials	Based on sub-group data, nalmefene plus psychosocial support is reported as dominant compared with psychosocial support alone, resulting in QALYs gained and reduced societal costs. The paper concludes nalmefene is cost effective from a UK societal perspective.	Study funded by Lundbeck. 4 authors: 1 Lundbeck employee; 3 employees of RTI Health Solutions (contracted by Lundbeck to support the study)
(Laramée et al., 2016b)	To assess the clinical relevance of the reduction in alcohol	Modelling study using pooled sub-group[1] data from the ESENSE 1, 2 and SENSE trials.	Based on sub-group data, the model predicted that 971 (95 % confidence interval	Study funded by Lundbeck.

	consumption in patients with a high or very high DRL that could be expected from the use of nalmefene plus psychosocial support compared with placebo plus psychosocial support		[CI] 904–1038) alcohol-attributable diseases and injuries and 133 (95 % CI 117–150) deaths would be avoided with nalmefene versus placebo (based on a cohort of 100,000). Concludes that reducing alcohol consumption with nalmefene plus psychosocial support is clinically relevant.	9 authors: 4 Lundbeck employees; 3 employees of Creativ-Ceutical (contracted by Lundbeck to support the study); 1 author with Lundbeck COIs (research consultancy, honoraria and travel support); 1 author declared there were no COIs.
(Laramée et al., 2016a)	To determine the cost-effectiveness of integrating nalmefene into the UK treatment pathway for alcohol dependence	Modelling study using pooled sub-group[1] data from the ESENSE 1, 2, and SENSE trials	Based on sub-group data, the paper reports that nalmefene plus psychosocial support produced greater QALY gains and lower costs compared with psychosocial support alone. Concludes that nalmefene represents a highly cost-effective treatment in this population.	Study funded by Lundbeck. 4 authors: 1 Lundbeck employee; 3 employed by RTI Health Solutions (contracted by Lundbeck to support the study)

[1] The sub-group are patients with a high or very high DRL at screening and randomisation.

3.3.4 Evidence from systematic reviews of nalmefene

Systematic reviews demonstrate a systematic approach to searching for and reviewing the evidence from different studies and are generally considered to be more robust evidence reviews (Hess, 2004; Ioannidis, 2016). Twelve systematic review papers (10 covering nalmefene efficacy in reducing alcohol consumption and 2 covering its safety) were identified (Table 7). Seven of the systematic reviews also included a meta-analysis, in which quantitative data from multiple studies are combined and analysed to produce an overall treatment effect (Ebrahim et al., 2016); this type of review is considered to be the 'gold standard' in evaluations of efficacy (Forsyth et al., 2014; Ioannidis, 2016; Palpacuer et al., 2019). The remaining five papers are based on narrative systematic reviews.

Considering firstly the systematic reviews with meta-analyses, the results on nalmefene differ depending on the study. Three report positive results for nalmefene in reducing alcohol consumption compared with placebo treatment: 'moderate' evidence was reported in the Jonas paper (although it also points out some limitations resulting from the methodology used) (Jonas et al., 2014); small but positive effects for nalmefene over placebo were reported in the study by Mann and colleagues (2016); and nalmefene was reported as superior to naltrexone in an indirect meta-analysis comparing the two drugs (Soyka et al., 2016), although issues with the reporting of this indirect meta-analysis have been raised (see note under Table 7). The other four systematic reviews with meta-analyses are more critical of nalmefene: a Cochrane review based on early nalmefene trials reported no significant effect for nalmefene over placebo in reducing alcohol consumption (Rösner et al., 2010b). Whilst two later studies (which include the Lundbeck trials data) report small but positive effects for nalmefene in reducing alcohol consumption, they conclude that this evidence is insufficient to recommend nalmefene (Palpacuer et al., 2015, 2017). The other meta-analysis concerned nalmefene safety and reported that nalmefene patients were no more likely than those on placebo to experience serious adverse events, although they were three time more likely to drop out of the studies due to adverse events (Johansen et al., 2017). The authors of this paper added some concerns about limitations in the safety data, including incomplete and inconsistent reporting and the short-term duration of the trials.

Five narrative systematic reviews were identified. One (Barrio and Gual, 2016) reported positive findings for 'patient-centred care' interventions in reducing alcohol consumption. In

this study, nalmefene was considered to be an example of a ‘patient-centred care’ intervention due to its ‘as-needed’ regimen. An expert review of biological treatments for alcohol dependence (Soyka et al., 2017) reported there was good evidence for nalmefene based on the evidence from the Lundbeck-sponsored trials. A review of nalmefene safety concluded that the drug can be safely used in patients, although higher instances of central nervous system problems (including dizziness, disorientation and insomnia) were experienced by the nalmefene patients (Sinclair et al., 2016). The other two narrative systematic reviews (Fitzgerald et al., 2016; Naudet et al., 2016a) draw attention to limitations of the nalmefene clinical trials, citing weak evidence for the drug and uncertainties about its value in treating alcohol dependence.

Table 7: Systematic review studies which include evidence on nalmefene

Study	Aims	Methods	Main findings on nalmefene	Funding source and COIs declared
Papers based on systematic reviews and meta-analyses (SRMA)				
(Rösner et al.,2010b)	To determine the effectiveness and tolerability of opioid antagonists in the treatment of alcohol dependence	SRMA of RCTs comparing opioid antagonists with placebo or active control. 50 RCTs included (1996 to 2010); 3 nalmefene studies included	No statistically significant effect for nalmefene over placebo in reducing alcohol consumption. Nalmefene patients had a mean difference of 4.7 fewer HDDs per month [95% CI: -12.38 to 2.98] and drank 4.16g less alcohol per day [95% CI: -32.69 to 24.37]	Support from Federal Ministry of Education and Research, Germany. 6 authors: 1 with Lundbeck COIs (speakers fees, consultancy, advisory board); other authors declare there are no potential COIs.
(Jonas et al., 2014)	To review the benefits and harms of medications for adults with AUDs	SRMA of FDA-approved and off-label medications. 122 RCTs and 1 cohort study included (1970 to 2014); 5 nalmefene studies included.	Nalmefene patients had on average 2 fewer HDDs/month [95% CIs: -3.0 to -1.0] and 1.02 fewer drinks per drinking day [95% CI: -1.77 to -0.28]. Concludes there is moderate evidence for nalmefene in improving some alcohol consumption outcomes	Funded by the Agency for Healthcare Research and Quality (AHRQ), US Dept of Health and Human Services. 11 authors; authors declared that there are no COIs.
(Palpacuer et al., 2015)	To review the risks and benefits of nalmefene as a treatment for alcohol dependence	SR (9 RCTs) and MA (5 RCTs) 9 nalmefene studies included.	Statistically significant effect for nalmefene over placebo in some alcohol consumption outcomes (nalmefene patients had on average 1.65 fewer HDDs/month at 6 months [95% CIs: -2.41 to -0.89] and 1.6 fewer HDDs/month at 1 year [95% CIs: -2.85 to -0.35] and 0.2g per day less alcohol consumption at 6 months [95% CIs: -0.3 to -0.10]. Concludes there is only limited efficacy for nalmefene due to small effect sizes and limitations in the trial data.	Supported by a grant from Rennes CHU (CORECT: COmité de la Recherche Clinique et Translationelle). Funders had no role in study design, analysis or manuscript preparation. 6 authors: authors declare that no authors have received funding from any company for the submitted work; 1 author has received travel, accommodations, expenses in relation to Lundbeck; he was invited by Lundbeck to present at a symposium in 2014, for which he declined any payment.

(Mann et al., 2016)	To present an overview of nalmefene's pharmacology and mechanisms of action and an analysis of its efficacy in the treatment of alcohol-dependent patients	SRMA of 7 nalmefene studies in reducing alcohol consumption in the 'intention to treat' (ITT) population and 4 examining efficacy in a 'target' (sub-group patients) population for whom nalmefene is licensed. Restricted to studies reporting a change from baseline in alcohol consumption.	The overall effect size in the 'ITT' population for reducing the number of HDDs was -0.2 [95% CI: -0.3 to -0.09] and in the target (sub-group) population was -0.33 [95% CI: -0.48 to 0.18]. Concludes that this MA confirms the efficacy of nalmefene in reducing alcohol consumption.	No funding was received for the paper. 7 authors: 2 Lundbeck employees; 5 with Lundbeck COIs (consultancy, speakers fees, honoraria, travel grants)
(Soyka et al., 2016)	To compare the efficacy and safety of naltrexone and nalmefene in reducing alcohol consumption.	An indirect MA of RCTs to compare naltrexone and nalmefene.13 naltrexone studies and 4 nalmefene studies included (ESENSE1, ESENSE2, SENSE and CPH-101-0801), including data from the nalmefene sub-group patients.	Reports that nalmefene was superior to naltrexone in reducing the quantity and frequency of drinking. The difference in favour of nalmefene was not statistically significant for frequency of drinking. The difference in favour of nalmefene was statistically significant (p=0.022) for quantity of drinking.[1]	Funded by Lundbeck 3 authors: 1 Lundbeck employee; 1 employed by the Institute for Applied Statistics (commissioned by Lundbeck to perform the analysis); and 1 with Lundbeck COIs (consultancy)
(Palpacuer et al., 2017)	To examine the efficacy of 5 drugs (nalmefene, naltrexone, acamprosate, baclofen and topiramate) in reducing TAC in patients with alcohol dependence who are still drinking.	SRMA of 32 RCTs published between 1994 and 2015. 9 nalmefene studies included	Authors report small but significant effects for nalmefene over placebo in the reduction of alcohol consumption. Nalmefene patients had 0.22 fewer HDDs/month [95% CI: -0.32 to -0.12], 0.26 fewer drinks per drinking day [95% CI: -0.48 to -0.05] and consumed 0.19g less alcohol per day [95% CI: -0.29 to -0.10]. Concludes there is no high grade evidence for nalmefene (or any of the drugs) in controlling alcohol consumption, and that studies are at a high risk of bias.	Funded by Rennes CHU (CORECT: Comité de la Recherche Clinique et Translationnelle 7 authors: authors declare that there are no COIs. 1 author has received travel, accommodations, expenses in relation to Lundbeck; he was invited by Lundbeck to present at a symposium in 2014, for which he declined any payment.
(Johansen et al., 2017)	To assess the harms associated with nalmefene use in patients with	SRMA of 15 published and unpublished RCTs. 8 RCTs provided the data for the meta-analysis	Compared with placebo, nalmefene patients were not statistically more likely to experience serious adverse events (Peto Odds Ratio = 0.97 [95% CI: 0.64±1.44]; p=0.86) but were three times more	Funded by the Head of Musculoskeletal Statistics Unit, The Parker Institute, Copenhagen University Hospital, Bispebjerg Frederiksberg. Also supported

	substance use or impulse control disorders.		likely to withdraw from a study due to adverse events (Peto Odds Ratio = 3.22 [95% CI: 2.46±4.22]; p<0.001). Concludes that the additional risk of withdrawal due to adverse events is a safety concern and should be explored via access to individual patient data.	by grants from The Oak Foundation. The authors declare that there are no COIs.
Papers based on narrative systematic reviews				
(Sinclair et al., 2016)	To review the safety and tolerability of pharmacological treatments for alcohol dependence	A 'comprehensive' review based on PRISMA guidelines covering all studies included in two previous Cochrane reviews published in 2010, studies collated for NICE CG-115 plus studies published since 2010 based on a systematic search. 8 nalmefene studies included.	Nalmefene described as having a similar safety profile to naltrexone but with higher reports of central nervous system problems (dizziness, disorientation, insomnia). Authors conclude nalmefene can be safely used in patients with alcohol dependence, including those with liver problems.	Funded by the University of Southampton. 4 authors: all with Lundbeck COIs (advisory board role, research grant, speakers fees, a part-funded studentship funded jointly by Lundbeck and Wessex Academic Health Sciences Network)
(Barrio and Gual, 2016)	To review the effectiveness of interventions which use a 'patient-centred care' approach in managing patients with alcohol dependence.	A narrative systematic review comprising 40 RCTs (5 based on pharmacological treatments and 35 on psychosocial interventions). Studies were selected if they demonstrated a 'patient-centred care' approach (individualised, respectful of the patients' own goals, and empowering). Pharmacological treatments selected were those using an 'as-needed' regimen. 3 nalmefene studies were included.	In relation to reducing alcohol consumption, the authors report mixed results for the psychosocial interventions and 'consistently positive' results for the pharmacological treatments reviewed. They conclude that 'patient-centred care approaches' may be beneficial in the reduction of alcohol consumption in patients with alcohol use disorder.	Funded by Lundbeck (including editorial support from a communications consultancy). Authors declare there are no COIs (but COIs relating to Lundbeck have been declared by these authors in previous publications (Gual et al., 2013; van den Brink et al., 2014a; Barrio et al., 2016).
(Fitzgerald et al., 2016)	To critically examine the evidence base for nalmefene and identify	A narrative systematic review of literature on nalmefene, based on a systematic search of published nalmefene	The authors report that efficacy data for nalmefene suffer from risk of bias from the conduct of the nalmefene trials: a lack of specification of a priori outcome measures and	No funding was received for the paper. The authors declare that there are no COIs.

	methodological issues relating to it.	studies, EMA documents, NICE appraisal documents and records from clinical trials databases. 144 records were examined.	sensitivity analyses; use of post-hoc sub-group analyses and the use of inappropriate comparators. The evidence for nalmefene in reducing alcohol consumption in patients with alcohol dependence is described as modest at best.	
(Naudet et al., 2016a)	To identify the evidence on the efficacy, effectiveness or efficiency of nalmefene in treating alcohol dependence.	A narrative systematic review of published and unpublished literature (up to April 2016), including clinical trials databases, regulatory body documents and the results from an earlier systematic review and meta-analysis (see Palpacuer et al., 2015). Includes a re-analysis of data used to indirectly compare nalmefene and naltrexone (contrasting with results reported by Soyka et al., 2016 above).	Reports that nalmefene demonstrates a small reduction in alcohol consumption but no evidence of 'harm reduction'; also reports that results are likely to be biased due to to attrition. Highlights that no studies have directly compared nalmefene with an active comparator; that post-approval clinical trials have not addressed the methodological issues identified in the literature; and that many nalmefene publications do not address limitations or methodological issues. Reports no significant difference between nalmefene and naltrexone in relation to their effect on quantity of alcohol consumed.	FN is funded by Laura and John Arnold Foundation, La Fondation Pierre Deniker and Rennes University Hospital, France (CORECT: COmité de la Recherche Clinique et Translationelle). The sponsors had no role concerning preparation, review or approval of the manuscript. 4 authors: 1 author has received travel, accommodations, expenses in relation to Lundbeck; he was invited by Lundbeck to present at a symposium in 2014, for which he declined any payment
(Soyka et al., 2017)	A review to inform a revised set of practice guidelines on the biological treatment of substance use and related disorders.	A narrative systematic review of publications between 2010 and 2015 on the biological treatment of patients with alcohol dependence. Evidence was evaluated by an expert group (the Task Force of the World Federation of Societies of Biological Psychiatry) and rated based on the strength of its evidence for efficacy. 6 published RCTs of nalmefene included.	A Category A rating was assigned to nalmefene, equating to full evidence from controlled trials. To be given this rating there had to be at least 2 or more double-blind parallel-group RCTs showing superiority to a placebo plus 1 or more positive RCTs showing superiority to or equivalent efficacy compared with a standard comparator treatment (where one exists). No discussion of data limitations or issues in relation to the RCTs was included.	Grants from the US NIAAA contributed to one author's contribution to the paper. 6 authors: 3 with Lundbeck COIs (advisory board, research support, consultancy, honoraria)

[1] The reporting from this indirect meta-analysis has been criticised for including results based on the nalmefene sub-group patients and comparing these with results from the total trial population for naltrexone studies (Naudet, 2016).

3.3.5 Further clinical trials of nalmefene

A search of the clinical trials databases (ClinicalTrials.gov; EU Clinical Trials Register; WHO International Clinical Trials Registry; and the ISRCTN registry) from June 2014 to September 2017 revealed that eleven further clinical trials involving nalmefene for the treatment of alcohol dependence have been registered. Of these, four are complete, three are active, two have been terminated due to problems in enrolling patients, and the status in two is unknown. Of the eleven trials, only three are RCTS of nalmefene efficacy in reducing alcohol consumption and all of these compare nalmefene with placebo treatment. Some of these trials have been conducted in alcohol-dependent patients with specific conditions including liver problems and borderline personality disorder and one (NCT02364947) has been conducted in the target group of patients for whom nalmefene is licensed (the sub-group patients). Six of the trials are sponsored by Lundbeck (Table 8).

Table 8: New clinical trials of nalmefene for the treatment of alcohol dependence

ClinicalTrials.gov identifier and study title	Study aim, population, recruitment and setting	Design	Study primary outcome measures	Results/Status	Funding source
NCT02197598 Exploratory, interventional, open-label, fixed-dose study with Selincro as-needed use, in alcohol-dependent patients with liver impairment	Aim: to explore the treatment effects of nalmefene in patients with alcohol-dependence who have liver impairment. Population: patients diagnosed with cirrhosis Recruited: 45	Single group assignment, open-label	16 listed covering alcohol consumption, DRLs, Clinical Global Impression Scale, Short-Form 36 Item Health Survey, liver functioning, and adverse events.	Study completed. Results made available on Eudra Clinical Trials website in Dec 2016; see https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-000413-31/results	Lundbeck
NCT02492581 Use of Selincro and Impact on Usual Practice (USE-PACT)	Aim: to evaluate the use of nalmefene in real life and its impact on alcohol consumption at one year. Population: Adult patients initiating nalmefene because of alcohol dependence. Recruited: 700	Non-randomised prospective cohort study in real life clinical settings	Relative change of TAC between inclusion and end of follow-up at one year.	Active, not recruiting. Estimated completion Feb 2018 No results posted.	University of Bordeaux (Sponsor) and Lundbeck (Collaborator)
NCT02372318 Single dose of nalmefene to modulate neural alcohol cue reactivity (NALCUE)	Aim: To use functional Magnetic Resonance Imaging (fMRI) to measure neural reactivity to alcohol-related and emotional cues in patients with alcohol dependence following a single dose of nalmefene 18mg. Recruited: 23	Randomised clinical trial	Difference in cue-induced brain activation between 2 fMRI scans (randomisation to nalmefene v placebo)	Study terminated. Reasons stated: recruitment target not reached within timeframe; missing data; low fMRI data quality.	Central Institute of Mental Health, Mannheim (Sponsor) and Lundbeck (Collaborator)
NCT02824354 Multicentre, Randomised, Double-blind, Placebo-controlled Trial of Nalmefene in Patients With Alcoholic Compensated Cirrhosis for the Treatment of Alcohol Dependence	Aim: to explore nalmefene treatment in patients with alcohol dependence diagnosed with alcohol cirrhosis. Recruitment: 250 estimated	RCT of nalmefene verus placebo	Reduction of the number of monthly HDDs after 6 months of treatment compared to baseline.	Status including recruitment unknown	Centre Hospitalier Universitaire, Amiens (Sponsor and collaborator)

NCT02195817 Interventional, open-label study of 18mg Selincro as needed use, in the treatment of patients with alcohol dependence in primary care	Aim: To determine the reduction in alcohol consumption in patients with alcohol dependence treated with 18mg Selincro as needed in conjunction with continuous psychosocial support in primary care. Recruited: 378	Non-randomised prospective cohort study in real life clinical settings in Europe	Change in the number of HDDs per month (baseline to month 3).	Study terminated due to enrolment challenges.	Lundbeck
NCT03034408 Effects of nalmefene and baclofen on impulsivity in subjects with alcohol use disorder and healthy control subjects	Aim: To examine the effect of nalmefene and baclofen on impulsivity in participants with AUD and healthy control participants. Recrutment: 60 estimated	Randomised, placebo-controlled, cross-over, single dose	1. Change in reaction time (0 and 2 hours post-dose) 2. Before-drug/after-drug difference in reaction time at Visits 2, 3 and 4.	Currently recruiting. Estimated completion Dec 2018	Prof. Daniele Zullino, University Hospital, Geneva (sponsor)
NCT02679469 A single centre, open-label, single-dose study investigating the safety, tolerability and pharmacokinetic properties of nalmefene 10mg tablets in healthy Japanese male subjects	Aim: To evaluate the safety, tolerability, and pharmacokinetics of nalmefene at a single oral dose of 10 mg in healthy Japanese male participants. Recruited: 7	Single-centre, open-label clinical trial	1. Measure the Maximum (Peak) Plasma Concentration of the Drug (Cmax) 2. Measure the Area Under the Concentration-time Curve From Time Zero to the Last Observable Concentration at Time t(AUCt) 3. Measure the Terminal-phase Elimination Half-life (T1/2) (Time Frame: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours post-dose)	Completed and has results (posted April 2017).	Otsuka Pharmaceutical Co Ltd (sponsor) and Lundbeck (collaborator)
NCT02752503 Nalmefene in alcohol dependence and borderline personality disorder	Aim: To study the effectiveness of nalmefene in decreasing alcohol intake in participants with AUD and comorbid BPD Recruitment: 30 estimated	RCT of nalmefene versus placebo	Primary outcome measures: Days of excessive (>60g for men and >40g for women) alcohol intake (Time Frame: 2 months)	Recruitment status unknown.	Fundacio Institut de Recerca de l'Hospital de la Santa Creu I Sant Pau (Sponsor) Hospital Universitari General de

					Catalunya (collaborator)
NCT02382276 A long-term extension study for the Phase 3 study of nalmefene in patients with alcohol dependence	Aim: To evaluate the long-term safety and efficacy of nalmefene 20mg in patients with alcohol dependence in a multi-centre, open-label, uncontrolled trial. Recruited:405	Non-randomised study (a continuation of NCT02364947	Primary outcome measure: number of participants with adverse events (24 weeks)	Completed and has results (posted 20 July 2020).	Otsuka Pharmaceutical Co Ltd (sponsor) and Lundbeck (collaborator)
NCT02364947 A multicentre, randomised, double-blind, placebo-controlled, 3-parallel-group comparison trial to investigate the effect of nalmefene on alcohol consumption reduction in patients with alcohol dependence (Phase 3 trial)	Aim: To evaluate the efficacy, safety, and dose-response of nalmefene hydrochloride at 10 mg and 20 mg in patients with alcohol dependence. Recruited: 678	RCT of nalmefene versus placebo	Change in number of HDDs/month from baseline (24 weeks). (19 secondary outcome measures listed).	Completed. Results posted 30 September 2019.	Otsuka Pharmaceutical Co Ltd (sponsor) and Lundbeck (collaborator)
NCT02639273 Effect of opioid receptor modulation on alcohol self-administration and neural response to alcohol cues in heavy drinkers: role of OPRM1 gene variation	Aim: To test nalmefene's effects on alcohol self-infusion and responses to alcohol cues. To test the role of different forms of OPRM1 on these effects Recruitment: 60 estimated	Randomised, cross-over assignment	Nalmefene-induced BOLD signal changes in neural regions associated with alcohol reward processing, including ventral triatum, amygdala, and insula (Time Frame: 1 hr post-study drug); nalmefene-induced changes in IV alcohol self-administration (Time Frame: 1 hr post-study drug)	Recruiting No results available. Completion date 2020.	National Institute on Alcohol Abuse and Alcoholism (sponsor)

Note: details were updated on 31/08/20

3.4 Critical examination of the Lundbeck trials of nalmefene

The three Lundbeck-sponsored RCTs are important because they formed the basis of the evidence on which nalmefene was approved by the EMA and recommended by the SMC and NICE. However, the results from these trials have been met with criticism by some reviewers, who have cited issues relating to the conduct, analysis and reporting of the trials. Weaknesses in the evidence base have been cited in a number of review papers (Palpacuer et al., 2015, 2017; Fitzgerald et al., 2016). The next few sections discuss the key points raised, and draw on recommendations for good practice in conducting and reporting clinical trials.

3.4.1 Pre-specification of outcome measures

Good clinical trial practice entails that all details of a clinical trial, including outcome measures, are pre-specified in a publicly available trial protocol, and on a clinical trials register, in advance of the trial starting (Schulz et al., 2010; Witkiewitz et al., 2015b). This is to avoid selective reporting of outcomes, a practice that may introduce bias into study findings (Dwan et al., 2014). Post-registration amendments were made to the outcome measures for all three nalmefene RCT protocols, including the addition of definitions of 'heavy drinking days' and 'total alcohol consumption' to the ESENSE 1 and 2 studies and the addition of an efficacy outcome for the SENSE study after the trial was completed (originally it included a safety outcome only) (Fitzgerald et al., 2016). Whilst revisions to these outcome measures were listed on one of the clinical trials registers (clinicaltrials.gov), they were not listed on the EU register (Fitzgerald et al., 2016). The CONSORT guidelines ask for authors to identify and explain changes to protocols, including any change to outcome measures (Moher et al., 2010). There is no mention of these changes in the trials papers, making it difficult for readers of the literature to to be aware of them.

3.4.2 Use of post-hoc sub-group analysis

The group for whom nalmefene is licensed and recommended is a sub-group of the original trial population used in the Lundbeck-sponsored RCTs (European Medicines Agency, 2013; NICE, 2014a). This sub-group comprised patients with a high or very high DRL (defined as drinking 60g or more per day for men and 40g or more per day for women) at both the screening and the randomisation stage of the trial process. The other trial patients (18% of the ESENSE 1 study and 33% of the ESENSE 2 study) had reduced their drinking to medium risk or below in the two-week period between their initial screening assessment and

randomisation, leaving little opportunity to make improvements in this group (Stevenson et al., 2015). It was for this reason that Lundbeck proposed to focus nalmefene on the sub-group patients – those still drinking at a high DRL at the randomisation stage (two weeks after their baseline assessment) (European Medicines Agency Committee for Medicinal Products for Human Use, 2012). The subsequent post-hoc sub-group analysis showed a greater effect of nalmefene compared with the effect in the total trial population, and this requirement (that nalmefene patients should be assessed after a two week period to check their drinking levels) was then included in the drug's licensing conditions (European Medicines Agency Committee for Medicinal Products for Human Use, 2012).

Reporting results for a sub-group of a trial population is not problematic in itself and has been described as a useful way to explore the heterogeneity of treatment effects in different patient groups (Sun et al., 2012). However, there are problems with conclusions which have been drawn from sub-group analyses which have not been pre-specified in an analysis plan; they have been described as misleading and likened to 'cherry picking' for the most favourable results (Brookes et al., 2001; Sun et al., 2012; Goldacre, 2013; Burke et al., 2015). Whilst these results may be useful in generating new hypotheses, they need to be tested and confirmed in further studies (Burke et al., 2015). The nalmefene trials were criticised for drawing conclusions about efficacy based on sub-group analyses which were not pre-specified (Palpacuer et al., 2015; Fitzgerald et al., 2016). However, the results based on this sub-group of patients have been presented as evidence for nalmefene efficacy in numerous other scientific papers, including the secondary analysis papers and some of the systematic reviews identified in this literature search (Sections 3.3.3 and 3.3.4). Since then there has been one trial (in Japan) to test the efficacy of nalmefene in the sub-group patients for whom it is licensed (see NCT02364947 and NCT02382276 in Table 8).

3.4.3 Missing data

Patients commonly drop out of clinical trials, leading to incomplete outcomes data, and a risk of bias in the results (Moher et al., 2010; Bell et al., 2014). Bias may occur when patients drop out because of how they respond to the treatment (Moher et al., 2010) and is viewed as particularly likely when more than 20% of patients drop out of a study (Dumville et al., 2006). In the Lundbeck-funded trials, between 35 and 53% of nalmefene patients dropped out (in the placebo group it was between 31% and 38%) (Gual et al., 2013; Mann et al., 2013;

van den Brink et al., 2014a). Several reviewers have highlighted the risk of bias this poses (Palpacuer et al., 2015; Fitzgerald et al., 2016).

Missing data in RCTs can be addressed in different ways – some studies have chosen to ignore cases with missing data, whilst others have performed calculations to estimate values for the missing data (known as 'imputation') (Moher et al., 2010; Bell et al., 2014). A simple form of imputation is to carry forward the last available observed data for a patient (known as 'last observation carried forward') (Bell et al., 2014), although this is not considered to be a robust approach (Moher et al., 2010). A technique called 'multiple imputation' is considered to be the least biased approach (Donders et al., 2006; Witkiewitz et al., 2015b), as it utilises multiple estimates and can account for variability in the data (Thabane et al., 2013). Where imputation is used, sensitivity analyses are needed to test the extent to which the results depend on differing assumptions made in analysing the data (including different ways of handling missing data) (Morris et al., 2014). As for sub-group analyses, it is good clinical trials practice to pre-specify planned and anticipated sensitivity analyses before data analysis begins (Chan et al., 2013; Thabane et al., 2013).

A range of techniques were used in the ESENSE 1 and 2 nalmefene trials to handle missing data, and sensitivity analyses were performed to test the impact of the different assumptions implicit in these techniques on the alcohol consumption results. However, these were not pre-specified (see Supplemental Information in Mann et al., 2013 and Gual et al., 2013) and have not consistently shown a positive effect for nalmefene over placebo (Stevenson et al., 2015; Fitzgerald et al., 2016), an issue noted by the EMA in its assessment of nalmefene (European Medicines Agency Committee for Medicinal Products for Human Use, 2012). No significant effect for nalmefene was noted in another review which used a conservative approach to imputing missing data (baseline observation carried forward) (Palpacuer et al., 2015). Although this approach assumes a 'worst-case' scenario in that patients' baseline drinking levels have not improved, the authors argue that this is appropriate to use where patients with side effects are excluded from the analysis (Palpacuer et al., 2015).

3.4.4 Comparators: use of a placebo rather than an active comparator (naltrexone)

According to the Declaration of Helsinki, new drug treatments should be compared with the best available alternative treatment currently used (World Medical Association, 2013). Studies comparing different treatments are important, as they allow clinicians to assess whether a new drug is superior to existing treatment options (Bourgeois et al., 2012).

Placebo-controlled studies are common, and this is thought to be due to a number of factors, including that they require smaller samples of patients, are less expensive, and are more likely than comparative studies to result in favourable findings for the drug being tested (Stafford et al., 2009; Bourgeois et al., 2012). However, all clinical trials of nalmefene have compared its efficacy with a placebo treatment, which has been criticised by some researchers who believe that it should have been compared with naltrexone, another alcohol dependence drug (Palpacuer et al., 2015; Fitzgerald et al., 2016; Naudet et al., 2016a). Although not licensed for the reduction of alcohol consumption (but for maintaining abstinence in patients who have withdrawn from alcohol), studies suggest that naltrexone has been used successfully 'off-licence' for this purpose (Maisel et al., 2013; Jonas et al., 2014). Furthermore, naltrexone has been recommended by NICE (2011) to control drinking in individuals with mild dependence who have either not responded to psychological interventions or who request a medication. Although some have argued that there are structural differences between the two drugs (van den Brink et al., 2014b) the clinical importance of these is unclear (Swift, 2013).

The lack of direct comparative effectiveness data on nalmefene and naltrexone was also an issue raised by the ERG for nalmefene (Stevenson et al., 2015). One possible solution is to conduct an indirect comparison, although at the time of the NICE assessment, Lundbeck stated that this would not be possible due to differences in the methodologies used in individual studies (NICE, 2014b). However, two indirect comparisons of these drugs have since been made, with differing conclusions (see Table 7 for details). One, funded by Lundbeck, controversially compared results from the nalmefene sub-group patients and naltrexone total patient population and concluded that nalmefene was superior to naltrexone (Soyka et al. 2016a); issues relating to the reporting of this study have been raised (Naudet, 2016). The other was a re-analysis using full data for nalmefene, concluding that nalmefene has no benefit over naltrexone (Naudet, 2016). It was the lack of evidence that nalmefene was better than any existing treatment which influenced the German Institute for Quality and Efficiency in Healthcare in its decision not to recommend nalmefene (IQWIG, 2014). The relatively higher cost of nalmefene compared with naltrexone has also prompted questions about whether scarce resources should instead have been focused on making psychosocial interventions more available (Spence, 2014). None of the new trials identified in the clinical trials registries (Table 8) compare nalmefene with any other active treatment (all are placebo studies).

3.4.5 Psychosocial intervention used

Patients in the Lundbeck-supported trials (nalmefene and placebo groups) received a psychosocial intervention to help them adhere to their medication and to reduce their alcohol consumption. Provision of psychosocial support alongside nalmefene treatment is also a requirement of the licensing conditions for the drug. The intervention used in the trials, termed BRENDA, was designed to be used in conjunction with pharmacotherapy for alcohol treatment and comprises six elements: a biopsychosocial evaluation; a report of findings from the evaluation given to the patient; empathy; addressing patient needs; providing direct advice; and assessing patient reaction to advice and adjusting the treatment plan as needed (Starosta et al., 2006). Because it has not been used as a standalone treatment in reducing alcohol problems, little is known about its effectiveness (Fitzgerald et al., 2016), although some studies suggest it can be used successfully in combination with pharmacotherapy (Pettinati et al., 2000; Garbutt et al., 2005).

Chapter 1 of this thesis (Section 1.3.2.2) outlined the range of NICE-recommended psychosocial support interventions used to address alcohol problems. However, BRENDA is not among these and it is argued that it is not sufficiently comparable to these (Fitzgerald et al., 2016). In the RCTs, BRENDA sessions were delivered weekly for the first two weeks and monthly thereafter (the initial session lasting 30–40 minutes and the remaining sessions 15–30 minutes), whilst NICE (2011) recommends more intensive psychosocial interventions delivered over 12 weekly sessions of 1 hour. Evidence from the Lundbeck-supported trials suggests that patients can significantly reduce their alcohol consumption when only receiving placebo and psychosocial support (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014a), suggesting the potential for psychosocial support to enable patients to reduce their drinking. Moreover, in one of the early trials (Anton et al., 2004) it was noted that nalmefene was not significantly superior to placebo in reducing alcohol consumption when compared with a more strongly evidence based psychosocial intervention (Fitzgerald et al., 2016). In their assessment of nalmefene, the ERG suggested that it would be more cost-effective to provide a NICE-recommended psychosocial intervention as a first level response, with nalmefene treatment offered to those who do not respond to this (Stevenson et al., 2015). However, it was anticipated that delivering the required level of psychosocial support to nalmefene patients in primary care would be challenging (Kerr, 2013), with efforts to implement even brief psychosocial interventions in primary facing barriers (Johnson et al.,

2010; van Beurden et al., 2012). An online support tool[6] was developed and made available to the NHS by Lundbeck due to these challenges in accessing psychosocial support, although little is known about the effectiveness of this tool or whether it has been evaluated.

3.4.6 Effect size for nalmefene

As mentioned in Section 3.4.5, there was a substantial and significant reduction in alcohol consumption among patients receiving placebo plus psychosocial support. For example, in the ESENSE 1 trial at six months, placebo patients had nine fewer monthly HDDs, whilst nalmefene patients had 11 fewer days (a difference in effect of 2 days per month). These small differences are present across all of the outcome measures in the Lundbeck-supported trials. Although in many cases these differences are statistically significant, there is debate about whether such small differences between the treatment groups are clinically meaningful. In the trial papers, authors argue that this difference is clinically relevant, on the basis that each heavy drinking day presents an increased risk of harm (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014a). Others argue that the effects are minimal and not clinically relevant, even where the more impressive sub-group results are considered (Spence, 2014). The issue of effect size was also debated by the EMA committee on nalmefene, who appointed an expert group to consider it further; their conclusion was that the effect size was modest but clinically relevant (European Medicines Agency Committee for Medicinal Products for Human Use, 2012).

3.4.7 Generalisability of nalmefene trials results

Clinical trials patients differ significantly from patients in real-world world clinical practice, raising questions about the wider applicability of trials results (Uijen et al., 2007; Hoertel et al., 2014). Patients may differ on a number of characteristics, including age, gender, disease severity and comorbidity (Moher et al., 2010). Other important differences which could impact on the applicability of RCT results arise from study settings and procedures used (including dose, timing and any additional therapies provided) (Rothwell, 2006; Moher et al., 2010). A number of issues relate to the applicability of the nalmefene trials to real world

[6] This online self-help support tool was developed by Lundbeck and called www.reduceyourdrinking.co.uk. It is unclear whether this online tool is still in use. The website does not appear when the URL is typed in a browser, but it is referred to in other online webpages, including some online pharmacies and discussion forums.

clinical practice, and to primary care in particular. Nalmefene was expected to be prescribed mainly in primary care (Lundbeck Ltd, 2012; Scottish Medicines Consortium, 2013; NICE, 2014b) and that is where marketing efforts were said to have been targeted (Fitzgerald et al., 2016; Spence, 2014). However, the trials were conducted mainly in patients from outside primary care and outside of the UK, used a form of psychosocial support not typically used in primary care, and were based on a highly specific patient group who may not be easily identified in primary care (Kerr, 2013; Drug and Therapeutics Bulletin, 2014; Palpacuer et al., 2015; Stevenson et al., 2015; Fitzgerald et al., 2016; Naudet et al., 2016). The short duration of the treatment period in the trials also raises questions about how long patients might safely use nalmefene (Drug and Therapeutics Bulletin, 2014).

3.5 Summary

Nalmefene is the latest alcohol dependence pharmacological treatment to be recommended for use in the UK NHS. It is recommended for use in patients with alcohol dependence but no withdrawal symptoms, and who are drinking at high DRLs (at initial assessment and 2 weeks later); it should also be prescribed in conjunction with continuous psychosocial support. Evidence contributing to the approval of nalmefene derives mainly from three Lundbeck-sponsored RCTs, which report that nalmefene is superior to placebo treatment in reducing alcohol consumption; the effects of nalmefene in this respect were greater in a sub-group of trial patients (defined post-hoc), and it is this sub-group for whom the drug was subsequently licenced. The nalmefene clinical trials failed to adhere to good practice measures relating to the conduct, analysis and reporting of clinical trials and their relevance to UK primary care (the target setting for prescribing nalmefene) is questionable. The uncertainties highlighted in this literature around the value and use of nalmefene in UK primary care have helped to inform the research questions for this study. These are listed below:

1. To what extent and how has nalmefene been prescribed in UK primary care?

2. How has nalmefene been marketed and what influence has this had on the way in which the drug is perceived and used in the UK?

3. What (other) factors have influenced nalmefene prescribing in UK primary care?

4. What are the perspectives of key stakeholders in the alcohol field regarding nalmefene, its promotion and its use in UK primary care?

4 METHODOLOGY

4.1 Introduction

The aim of this study is to describe patterns of nalmefene prescribing for alcohol problems in UK primary care, and understand factors which may have influenced these. To achieve this aim, a mixed-methods approach has been used, involving quantitative and qualitative data collection and analysis across three individual study strands – a quantitative analysis of GP prescribing data (Study 1); a qualitative documentary analysis of nalmefene marketing activities (Study 2); and qualitative interviews with a range of professionals working in the alcohol field (Study 3) (see Chapters 5, 6 and 7). These studies have all been informed by a review of the nalmefene evidence, based on a systematic literature search.. This chapter starts by introducing the mixed-methods approach to conducting research, and factors which might have an impact on the approach taken. The next section will outline how a mixed-methods approach has been used in this study of nalmefene use in UK primary care. This includes an overview of the mixed-methods study design, including how the separate study strands connect with each other and how the mixed-methods analysis will be performed. Detailed information on the data collection, analysis methods, and ethical considerations relating to each study strand is embedded within their respective chapters (Chapters 5, 6 and 7).

4.2 A mixed-methods approach

Mixed-methods studies draw on both quantitative and qualitative methods to understand a research problem. A mixed-methods approach involves "*research in which the investigator collects and analyses data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or a program of inquiry*" (Tashakkori and Teddlie, 2013, p. 4). They add that integration is a key factor in the research design, as it is the meaning generated from the integrated results which makes the mixed-methods approach more than just the product of employing a qualitative and a quantitative method. Mixed-methods studies are useful in a variety of circumstances, including where one data source alone is unable to address the overall research question; where there is a need to explain initial findings; and where there is a need to generalise exploratory findings (Creswell and Plano Clark, 2011). Mixed methods can thus offer a more complete account of a research topic; an opportunity to understand a research problem from different perspectives or worldviews; and a way to contend with the limitations inherent in a

purely quantitative or purely qualitative approach (Creswell, 2009; Creswell and Plano Clark, 2011; Bryman, 2012).

4.3 Influences on mixed-methods research designs

Research designs do not exist in a vacuum and are shaped by a range of different factors. Four key influencing factors that can shape research design are outlined by Bryman (2012): philosophical underpinnings; theory; practical considerations; and values.

4.3.1 Philosophical underpinnings: the role of ontology and epistemology

A research design can be underpinned by varous philosophical perspectives relating to how we view the world (ontology) and how we learn about it (epistemology) (Creswell and Plano Clark, 2011; Bryman, 2012). Research questions, methods and analysis techniques can therefore be influenced by particular ontological and epistemological standpoints (Bryman, 2012), and it is argued that the role of these perspectives should be acknowledged in research studies (Creswell and Plano-Clark, 2011).

The acceptibility of mixing quantitative and qualitative approaches in one single study has been questioned on the basis that the two approaches derive from completely different paradigms and philosophical assumptions (Smith, 1983; Guba, 1985; Denzin, 2010). Before discussing the philosophical assumptions underpinning a mixed-methods approach, it is useful to first consider how these apply to quantitative and qualitative methods of inquiry. These two methods are said to be underpinned by opposing views about the social world (ontology). Quantitative research is rooted in 'objectivism', where social entities are viewed as existing independently of social actors, whilst qualitative research is rooted in 'constructivism', whereby social phenonema are viewed as being shaped by social interaction and changed by social actors (Creswell and Plano Clark, 2011; Bryman, 2012). Their epistemological positions (how knowledge is acquired) reflect these different ontological perspectives. Quantitative research is generally associated with a natural science model of learning about the world ('positivism'), where knowledge can be confirmed by the senses, and where the aim of research is to test a hypothesis (a deductive approach) (Creswell and Plano Clark, 2011; Bryman, 2012). By contrast, qualitative research assumes an interpretivist lens, where social phenomena are interpreted from the viewpoints of social actors. Bryman (2012, p. 30) describes interpretivism as follows: "*it is the job of the social scientist to gain*

access to peoples' 'common sense thinking' and hence to interpret their actions and their social world from their point of view".

Although mixed-methods studies draw on both quantitative and qualitative approaches, some writers have argued that they are underpinned by their own particular philosophy or worldview. For some, the worldview with which mixed-methods approaches align most closely is 'pragmatism' (Rossman and Wilson, 1985; Tashakkori and Teddlie, 2003; Creswell and Plano Clark, 2011). A pragmatic approach is one which places priority on the research question and which of the available methods are the most suitable for addressing this (Creswell and Plano Clark, 2011). For the pragmatist, acquiring knowledge about the world should be driven by a practical need to collect data which can answer a research question. This is illustrated by Creswell and Plano-Clark (2011, p. 46), who argue that pragmatism is an appropriate worldview for mixed-methods research, "*because it enables researchers to adopt a pluralistic stance of gathering all types of data to best answer the research questions*".

4.3.2 Theoretical drivers of research design

Research designs can also be influenced by theory (Bryman, 2012). For example, theory can influence a researcher to take a particular stance on a topic, which can then act to guide or direct the phases of a mixed-methods study (Creswell and Plano Clark, 2011). The theory relating to a topic can present itself in a variety of ways , including through the research literature, which may serve to highlight gaps in knowledge or inconsistencies in the research topic (Bryman, 2012). Theory may also be applied through the use of conceptual models or use of theories to help explain research findings (Creswell and Plano Clark, 2011). Where theory has guided a study, this is sometimes known as a 'deductive' approach, where the aim is to test the theory; in contrast, studies that aim to develop theory are 'inductive' in nature.

Just as philosophical perspectives differ for qualitative and quantitative methods, so too does the role of theory, with quantitative studies tending to be more deductive in nature and qualitative studes tending to be inductive (although theories can also be tested using qualitative methods) (Bryman, 2012). Mixed-methods studies can therefore draw on both deductive and inductive approaches to theory (Creswell and Plano Clark, 2011).

4.3.3 Practicalities and research design

Practical considerations can have a considerable influence on research design. Aside from a need to select a research design which will address the study aim and research questions, other considerations may relate to the nature of the topic being studied and the population of interest. Some approaches or methods may not be suitable or practical when applied in particular circumstances (Bryman, 2012).

Issues such as available time and resources may apply particularly to mixed-methods research because of the multiple methods used (Creswell, 2009). It is recommended that the feasibility of collecting quantitative and qualitative data should be considered at an early planning stage of the project (Creswell and Plano Clark, 2011), to assess the time and resources required to gain approval for the various strands; to gain access to participants; and complete the data collection and analysis for each strand. The involvement of a team of researchers can be beneficial for mixed-methods studies that require a range of different skills (Creswell and Plano Clark, 2011).

4.3.4 Values and research design

Researchers have their own values and beliefs which may affect how a study is conducted, regardless of whether it employs mixed methods or not. These can impact on research topics, research questions, data collection, analysis and the interpretation of the findings (Bryman, 2012). It is recommended that researchers include their reflections on possible biases when they write about their studies, a process commonly known as 'reflexivity' (Finlay, 1998). This is addressed later in this chapter in relation to this study.

4.4 Using a mixed-methods approach to study nalmefene prescribing

This section discusses the key influences on the study research design, explains the rationale for using a mixed-methods approach, and outlines the study research design and the method used to analyse and interpret the data.

4.4.1 Key influences on research design

The approach taken in this thesis was applied, and did not draw upon any particular theoretical framework. However, issues raised in the available literature on nalmefene (Chapter 3) have informed the overall focus of the study as well as the specific research questions (Table 9). The literature revealed mixed views about the potential value of

nalmefene, concerns about the conduct and reporting of the RCTs, and uncertainties and concerns about how nalmefene might be used in the primary care setting (Kerr, 2013; Spence, 2014; Palpacuer et al., 2015; Fitzgerald et al., 2016; Mann et al., 2016; Naudet et al., 2016a, 2016b; Soyka et al., 2016). Critics raised questions about the regulatory approval of nalmefene (Spence, 2014; Naudet et al., 2016c) and commented that the drug was 'heavily marketed' towards primary care prescribing (Fitzgerald et al., 2016). The issues raised in the literature have highlighted a need to understand how nalmefene has been used in UK primary care and which patients have received it and to understand what factors may have influenced the uptake of nalmefene.

The key drivers of the study design were the overall aim and the specific research questions to be addressed, which required a mix of qualitative and quantative methods. As the prescribing period of interest (from May 2013, when nalmefene was launched) pre-dates the commencement of this study, a retrospective approach to understanding nalmefene prescribing was adopted. This included the use of data from electronic health records, which have been used widely to study prescribing practices retrospectively (Gama, 2008; Herrett et al., 2015; Lao et al., 2016; Curtis et al., 2019; Jani et al., 2020). It also relied on qualitative interviews with participants to recall events which occurred in the past. The advantages and disadvantages associated with these approaches will be discussed in Chapters 5 and 7. The specific analyses performed on the prescribing data were guided by informal discussions held with key informants as well as factors identified in the nalmefene literature, for example, the anticipated challenges for GPs in prescribing according to the the licensing conditions for nalmefene (Kerr, 2013; Fitzgerald et al., 2016). In this study, the prescribing data alone could not answer all of the study research questions, and thus a qualitative component was needed to help understand prescribing patterns from the perspective of individuals working in the field of alcohol treatment.

Although numerous factors are likely to influence prescribing behaviour, two specific factors identified in the literature and explored in this study include the NICE guidance approving nalmefene and pharmaceutical marketing activities. The influence of NICE guidance on primary care prescribing has been reported in previous studies (Wathen and Dean, 2004; Curtis et al., 2018) and the NICE approval of nalmefene was queried by some critical reviewers (Fitzgerald et al., 2016; Naudet et al., 2016c). Research on pharmaceutical marketing suggests that promotional activities can influence prescribing behaviour (as

discussed in Chapter 2); authors of some critical reviews of nalmefene had commented that the drug had been heavily marketed towards primary care (Spence, 2014; Fitzgerald et al., 2016). The role of both of these potential influencers on nalmefene prescribing has been explored via quantitative and qualitative methods. The influence of the NICE recommendation on national prescribing levels was tested quantitatively via a time series analysis. The impact of marketing activity was not quantitatively tested in this way because, unlike regulatory approval, which is at a national level, it was difficult to define a national 'marketing' event to explore quantitatively. Although formally 'launched' in the UK in May 2013, no nalmefene prescribing data were available before this time, making the impact of a formal launch on prescribing untestable. It was therefore necessary to explore the impact of marketing activity in another way; this was done qualitatively via a documentary analysis (Chapter 6) and semi-structured interviews (Chapter 7).

The study is underpinned by a pragmatic approach, in that it uses the most suitable and available methods for addressing the aims and research questions. However, the different study strands are underpinned by differing ontological and epistemological perspectives. For example, the quantitative strand draws on positivism in the analysis of nationally representative data on nalmefene prescribing. The qualitative phase draws on an interpretivist approach in which prescribing patterns and influences are explored from the perspectives of the participants. However, there is not always a clear distinction between quantitative and qualitative methods in their ontological or epistemological stances according to Bryman (2012, p. 26), who writes that these philosophical perspectives are more 'free-floating' and driven more by practical considerations. A range of ontological and epistemological stances may be identified within one study. For example, while the documentary analysis (Chapter 6) employs a qualitative approach overall, it could be argued that positivist principles have been used in the analysis, including the quantification of scientific papers with industry conflicts of interest and the involvement of a second researcher in checking a sample of the data extractions.

Practical contraints relating to time, skills and resources have also shaped this study design. For example, obtaining patient-level data for research was both time-consuming and financially expensive. Scoping time had to be factored into the study at the planning stage in order to identify and research available options and their financial costs. Budgetary restraints meant that only a limited amount of prescribing data could be purchased, which placed

limitations on how some of the quantitative analyses were conducted. Patient-level data were complex and required significant data management time, resulting in limited time for data analysis and write up. Similarly, time constraints meant that some boundaries had to be set for the type of materials included in the documentary analysis (for example, it was not possible to include conference abstracts, commentaries, editorials and media reports).

4.4.2 Rationale for adopting a mixed-methods approach

There are a variety of reasons for conducting mixed-methods research, as outlined above (i.e., see Bryman 2012, p. 633). This study aims to explore nalmefene prescribing in primary care – a natural phenomenon that is also complex and multifaceted. This requires a set of research questions and methods that can uncover both 'what' happened and 'why' it happened. For example, the quantitative prescribing data provide information about levels of nalmefene prescribing, who has been prescribed the drug, and some contextual details around this. The qualitative interview data help to explain levels of prescribing and why nalmefene may have been prescribed that way. An additional qualitative documentary analysis of marketing activities was included to explore the potential role of marketing in influencing the uptake of nalmefene. Although marketing was also explored in the qualitative interviews, this documentary analysis was conducted to provide more detailed, more complete data on the range of marketing activities undertaken, reflecting the potential influence of pharmaceutical marketing, as discussed in Chapter 2.

4.4.3 The mixed-methods study design

A variety of different mixed-methods study designs have been outlined in the literature (Creswell and Plano Clark, 2011; Bryman, 2012). These can be distinguished according to a number of factors including: the level of interaction between the quantitative and qualitative strands (whether this occurs only at the end of the study when the data from all strands are integrated or whether there is interaction between strands at an earlier stage); the relative importance of the strands in contributing to the study (whether one particular strand is the main contributor or whether all strands are equal in importance); the sequence in which the data for different strands are collected (whether one strand follows on from another, or whether they are conducted concurrently); and how the data from the separate strands are mixed (and at which point) (Creswell and Plano Clark, 2011; Bryman, 2012). Of paramount importance is that the mixed-methods design selected is appropriate for the purpose of the study (Creswell and Plano Clark, 2011).

This mixed-methods study consists of three strands :

- Study 1: A quantitative analysis of GP prescribing data (Chapter 5)
- Study 2: A qualitative documentary analysis of nalmefene marketing activities (Chapter 6)
- Study 3: Qualitative interviews with a range of professionals from the alcohol field (Chapter 7)

Table 9 lists the key study questions and how data from across the three study strands contribute to answering these. For some research questions, data from multiple strands are used.

Table 9: Study research questions and methods

Research questions (RQs)	Methods	Chapters
1. To what extent and how has nalmefene been prescribed in UK primary care?	Quantitative data analysis of GP prescribing data (Study 1): National level prescribing data is used to describe general patterns and trends Patient-level data from CPRD have been used to examine which patients have been prescribed nalmefene Qualitative interviews (Study 3) to gain insights into levels of nalmefene prescribing, and how it has been used in clinical practice.	Chapter 5 (Quantitative Analysis) Chapter 7 (Qualitative interviews)
2. How has nalmefene been marketed and what influence has this had on the way in which the drug is perceived and used in the UK?	Documentary analysis (Study 2) of nalmefene promotional activities identified from the systematic literature review and grey literature to identify the range of activities, who was involved and key messages used Qualitative interviews (Study 3) with professionals working in the alcohol field to obtain data on their experiences and perceptions of nalmefene promotional activities	Chapter 6 (Documentary analysis) Chapter 7 (Qualitative interviews)
3. What (other) factors have influenced nalmefene prescribing in UK primary care?	Quantitative data analysis of GP prescribing data (Study 1) to examine the impact of the NICE guidelines on national nalmefene prescribing levels Qualitative interviews (Study 3) to obtain data on which factors (facilitators and barriers) are perceived to have influenced nalmefene prescribing in UK primary care	Chapter 5 (Quantitative analysis) Chapter 7 (Qualitative interviews)
4. What are the perspectives of key stakeholders in the alcohol field regarding nalmefene, its promotion and its use in UK primary care?	Qualitative interviews (Study 3) with key stakeholders to obtain data on: Views about the value of nalmefene and its licensing conditions Prescribing experiences Perceptions of nalmefene implementation and uptake in primary care Experiences and perceptions of nalmefene promotional activities	Chapter 7 (Qualitative interviews)

This study design (illustrated in Figure 2) draws on elements of two mixed-methods models – the sequential explanatory model and the convergent model (Creswell and Plano Clark, 2011). Firstly, at an early stage, findings from the literature review and the quantitative strand (Study 1) helped to inform the questions included in the topic guide for the qualitative interviews (Study 3). This part of the study design may be described as following a sequential

explanatory model. The aim was to to generate qualitative insights from participants which might explain and add context to some of the patterns identified in the prescribing data. Table 10 outlines the ways in which the prescribing data findings informed the qualitative topic guide. In convergent models, the main purpose is to integrate data or findings from across multiple study strands to generate a more comprehensive understanding of a research topic (Bryman, 2012). The components of a convergent model also apply to this study design – the data collection and analysis for each study strand was conducted separately initially and findings and conclusions from all three studies were integrated at the end of the study to generate a more comprehensive understanding of nalmefene (Chapter 8).

Figure 2 illustrates that the findings from all three studies contribute to a convergent analysis at the end of the study. The connections between the literature review (Chapter 3) and between the different studies during the course of the research are also highlighted and include:

- The nalmefene literature has influenced all of the other studies. The literature contained concerns that GPs may find it difficult to prescribe the drug in line with its licensing conditions and also included claims that nalmefene could engage new patients into treatment. Both of these issues were explored in the prescribing data (Study 1) and the qualitative interviews (Study 3). The literature also highlighted that there were mixed views about the evidence for nalmefene, and this too was explored in the qualitative interviews (Study 3). Finally, many of the scientific papers identified in the literature review were used in the documentary analysis (Study 2).

- Some of the findings from the prescribing analysis (Study 1) informed the qualitative data collection (Study 3), as outlined in Table 10.

- Finally, the early scoping work for the documentary analysis (Study 2) helped to identify some potential participants for the qualitative interviews, who were able to comment on marketing activities for nalmefene (Study 4).

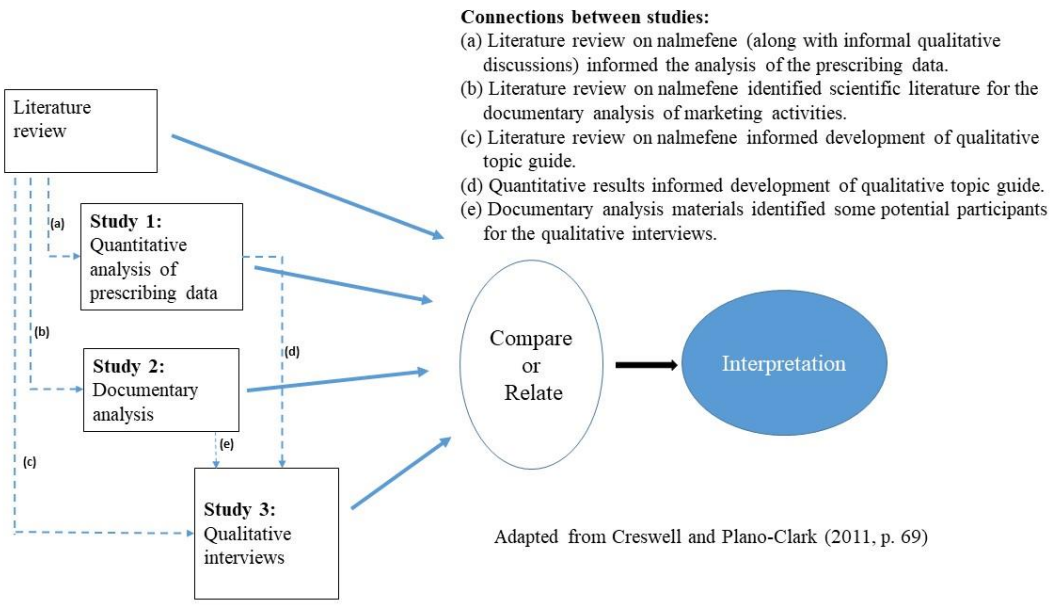


Figure 2: An illustration of the research design including connections between studies

Table 10: How quantitative findings (Study 1) were explored in the qualitative phase (Study 3)

Findings from Study 1 (prescribing data analysis)	**How quantitative findings were explored in Study 3 (qualitative interviews)**
UK-level data on prescribing suggests uptake has been low in primary care	Participants were asked about levels of nalmefene use generally and possible explanations for this. If not already mentioned, they were prompted on the role of the licensing conditions, the setting for prescribing (primary care versus specialist services), identification of patients, the evidence on nalmefene and the goal of nalmefene (reduction rather than abstinence) *"How widely do you think nalmefene is used in the UK or more locally?"* *"Why do you say that?"*
Patient-level data suggest many nalmefene patients do not align with the licensed patient group for nalmefene	The qualitative interviews were used to explore views about the licensing conditions and how these worked in clinical practice. Prescribers were asked about patients who had received nalmefene: *"Can you talk me through how you prescribed the drug?"* (Prompts included: adherence to licensing conditions, including psychosocial support provided) All participants were asked about the licensing conditions more generally: *"What are your views on the nalmefene licensing conditions?"* (Prompts included: how these work in practice; prescribing within these and prescribing outwith these and views about this) All participants were prompted on the role of the licensing conditions in explaining levels of nalmefene prescribing: *"How widely do you think nalmefene is used in the UK or more locally?"* *Why do you say that?"* (prompt on licensing conditions)
Patient-level data suggest nalmefene is prescribed to a range of patients, half of whom had previously engaged with treatment.	Participants who had prescribed were asked what sort of patient received nalmefene – whether they were new to treatment or had prior experience of treatment: *"What kind of patients did you prescribe to?"* (Prompts included whether patients were newly presenting or had already received treatment)
Most nalmefene patients only received one prescription	Prescribers were asked about duration of prescribing in their patients, including whether patients got more than one prescription: *"Can you talk me through how you prescribed the drug?"* (Prompts included number of prescriptions issued and whether patients received more than one)

4.4.4 Mixed-methods data analysis and interpretation

The data collected in each of the study strands were first analysed and interpreted independently (see Chapters 5, 6 and 7 for details of data collection methods, analysis and results), which is the first step in mixed-methods data analysis (Creswell and Plano Clark, 2011). The second step is to integrate the findings from each study strand. To achieve full integration in mixed-methods research, the aim is not merely to add the findings from both types of data together, but to generate an enhanced understanding based on synthesised results (Bryman, 2012), an aim which some mixed-methods research has failed to do properly (O'Cathain et al., 2008; Bryman, 2012). The integration of findings in this study has occurred at two stages. First, research from the quantitative study informed the development of the qualitative topic guide, allowing a 'connected' analysis (Creswell and Plano Clark, 2011) to assess the extent to which the themes generated in the qualitative study helped to explain some of the findings reported in the quantitative study and whether the additional follow-up data provide a better understanding of the problem than the quantitative results alone. The second stage of integration was at the end of the study and involved a 'merging' analysis (Creswell and Plano Clark, 2011). Results and inferences relating to each of the research questions were extracted from across the studies and displayed side-by-side in tabular form. The side-by-side findings and inferences were compared and contrasted, and analysed to generate 'meta-inferences' (Tashakkori and Teddlie, 2013). The results of the mixed-methods analysis are presented in Chapter 8 (Discussion), including discussion of how the study results relate to the wider literature.

4.5 Reflections on the role of the researcher in the study

In considering the methods used in this PhD study, it is also important to provide some initial reflections on my role as researcher. Before starting this PhD, I worked as researcher in a non-profit social research institute independent of government and academia and was involved in a range of quantitative and qualitative studies for various clients. Through this role I acquired a broad set of skills, mostly in managing and analysing large-scale population surveys, but also, some qualitative research experience, primarily in evaluations of interventions. The potential to build on both my quantitative and qualitative research experience was one of the reasons I decided to pursue a PhD. My knowledge of research management, processes and skills has been valuable in helping me to plan and conduct the research for this mixed-methods thesis. In particular, my experience of using quantitative

datasets has been beneficial in managing and analysing the prescribing data. This included the need for a systematic approach in all aspects of this, including data quality checks and keeping records of data management tasks and analyses. However, for this thesis, I was also required to develop new skills in a number of methodological areas (including time series analysis, management and analysis of patient-level prescribing data, and documentary research). Furthermore, as I had no prior experience of research on the topic of nalmefene or alcohol treatment, the initial stage of the study involved extensive background reading of the literature on alcohol treatments, clinical trials and pharmaceutical marketing.

It is also worth reflecting on any sources of possible bias in the thesis. The justification for this study is to generate knowledge and understanding about the use of a drug which is viewed as controversial. It builds on research conducted by one of my academic supervisors (Professor Niamh Fitzgerald), which has taken a critical stance on nalmefene (Fitzgerald et al., 2016). There is therefore a potential for this to have influenced my views about the drug and how the study should be conducted, especially in relation to interpreting the qualitative findings, which are more open to influence by researcher values and beliefs (Creswell, 2009). When I applied for this PhD I had no prior knowledge of nalmefene or any controversy around it, and very little knowledge of alcohol treatment approaches. My interest in applying for this particular PhD was related to the general topic area of alcohol research. I had previously worked on studies relating to population-level approaches to addressing alcohol problems (including attitudes to minimum unit pricing and the implementation of the alcohol licensing legislation) and was interested in expanding my research knowledge to include alcohol treatment. I had no strong views about which particular alcohol treatment interventions should be made available to individuals and, on balance, I feel that I have managed to retain some degree of objectivity in discussing the merits of different approaches to treating alcohol dependence.

4.6 Summary

In summary, this thesis aims to describe patterns and understand influences in nalmefene prescribing in UK primary care. Four specific research questions have been addressed, using a mainly convergent mixed-methods design consisting of three study strands. The first is a quantitative analysis of primary care prescribing data which describes levels of prescribing, explores the impact of the NICE guidelines on these levels, and describes how nalmefene has been prescribed to individual patients. The second, a documentary analysis of nalmefene

marketing activities, describes the range of activities undertaken, key messages relayed about nalmefene, and who was involved. The third, a qualitative study, was designed to obtain the perspectives of key professionals working in the alcohol field about nalmefene, its promotion and use in UK primary care. The following three chapters (Chapter 5, 6 and 7) now present the methods, analysis and results for each of the studies.

5 STUDY 1: NALMEFENE PRESCRIBING IN UK PRIMARY CARE

5.1 Introduction

This study uses GP prescribing data to understand how nalmefene has been used in UK primary care. The literature discussed in Chapter 3 suggests there are mixed views about the value of nalmefene in treating alcohol dependence; concerns about the strength of the evidence from the clinical trials; and potential challenges for GPs in prescribing it in line with its licensing conditions.[7] Primary care had been proposed as the most appropriate setting for prescribing nalmefene, and it was proposed that the drug could engage a new cohort of patients into alcohol treatment (Lundbeck Ltd., 2012; Gual et al., 2013; Mann et al., 2013; NICE, 2014b; van den Brink et al., 2014a). This chapter presents an analysis of UK primary care prescribing data, including national levels and trends (including the influence of the NICE Technology Appraisal (TA) on nalmefene) (NICE, 2014a) and an analysis of how the drug has been prescribed to patients in real-world clinical practice. The extent to which nalmefene patients align with the licensed patient group for the drug, the broader clinical trials population and the marketing claim about potentially engaging new patients into treatment, is also discussed.

Three specific questions will be answered:

- What are the patterns and trends in nalmefene prescribing in primary care at a national[8] level (Section 5.2)?
- To what extent are changes in levels of prescribing associated with the publication of the NICE TA recommending nalmefene as an option for treating individuals with alcohol dependence (Section 5.3)?
- How have GPs used nalmefene for individual patients (Section 5.4)?

[7] Patients with alcohol dependence, who are without physical withdrawal symptoms and who do not need immediate detoxification, and who continue to drink at a high DRL 2 weeks after an initial assessment. It is only to be given with continuous psychosocial support.

[8] Note that the data used to analyse monthly trends in prescribing is based on English practices only.

5.2 National-level nalmefene prescribing patterns and trends

5.2.1 Aim

This analysis aims to explore and describe nalmefene prescribing patterns at a national level, including general trends and patterns in the monthly number of items prescribed, number of GP practices prescribing, and number of Clinical Commissioning Groups (CCG)[9] prescribing.

5.2.2 Methods

5.2.2.1 Data source and structure

Data were obtained from the OpenPrescribing.net database (*OpenPrescribing.net*), a publically available web-based data resource which utilises anonymised published NHS data on prescribing by all registered GP practices in England. The extracted data included all prescriptions dispensed between May 2013 and January 2017 for prescribing of nalmefene (using BNF code 0410010D0). It presented the number of nalmefene 'items' prescribed (and subsequently dispensed) per month at individual GP practice level and at CCG level. An 'item' is the equivalent of a prescription, and can vary in the quantity (i.e., the number of tablets or boxes) of the medication prescribed (Curtis and Goldacre, 2018). The data also included quantity of tablets prescribed, prescribing month, general practice name, the name of the CCG area to which that practice belonged, and practice type (see Section 5.2.2.2). Only GP practices who have prescribed nalmefene appear in the dataset. The data were supplied as an Excel file comprising 5987 rows of data, each row representing a prescribing entry giving the total number of nalmefene items prescribed by a GP practice in a particular month.

5.2.2.2 Data management

Basic tables describing variables in the dataset were created to conduct initial quality checks on the data. Each row of data was checked to ensure it respresented a unique monthly prescribing figure for each practice. Duplicate rows (*n*=46), where more than one row of prescribing data was present for a GP practice in one month, were identified. This was due to a small number of practices (*n*=32) using multiple drug names to record their nalmefene

[9] CCGs were established in England in April 2013, to plan and commission health services for a local area. At the time of receiving the data, there were 206 CCGs operating. See https://www.nhscc.org/ccgs/

prescribing – for some items they used the generic name 'nalmefene', and for others they used the brand name 'Selincro', resulting in two separate prescribing entries appearing for that month. Once identified and checked with the team at OpenPrescribing, these separate entries were merged to form an aggregate item count prescribed for that practice in that month, leaving 5941 rows in the dataset.

The dataset comprised 1756 unique prescribers, classified into eight different practice types. Most were were 'standard' GP practices (*n*=1666) and the remaining 90 comprised a variety of other prescribing institutions, including those from community and public health services (Appendix 2, Table 1). The practice type variable was recoded to divide prescribers into 'standard' GP practices (code 4 in the general practice data from NHS Digital[10]) and 'non-standard' practices (covering all other prescribers). As it is unclear how well these types of organisation are represented in the monthly prescribing data, this analysis will focus on the 'standard' GP practices, in line with other studies of drug utilisation (Curtis et al., 2018, 2019). However, some brief discussion of prescribing done within these other environments is included in the results.

Count variables were constructed to calculate monthly totals for the number of nalmefene items prescribed, the number of prescribing GP practices, and the number of prescribing CCGs. Counts of GP practice and CCG are based on their practice and CCG 'code' rather than 'name' as the 'code' variables do not have missing data.

5.2.2.3 Data analysis

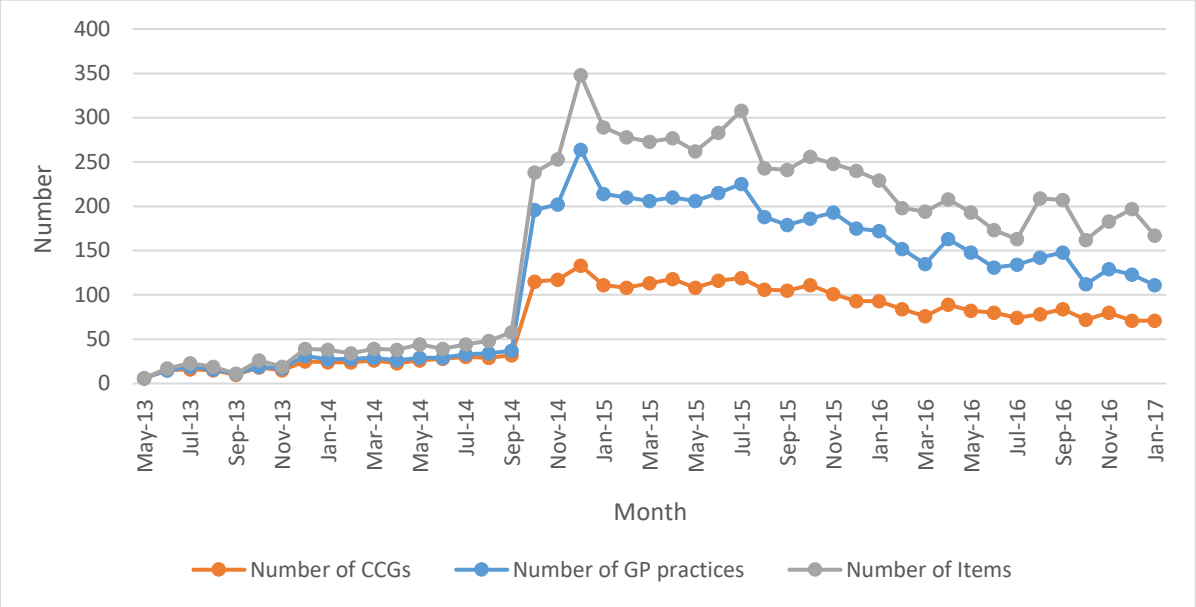
Data were analysed using Microsoft Excel, describing overall patterns and trends in nalmefene prescribing.

5.2.3 Results

Between May 2013 and September 2014, a small number of nalmefene prescriptions were recorded. There was a steep increase in October 2014, with later peaks in December 2014 and July 2015, after which a general downward trend occurred. The number of prescribing GP

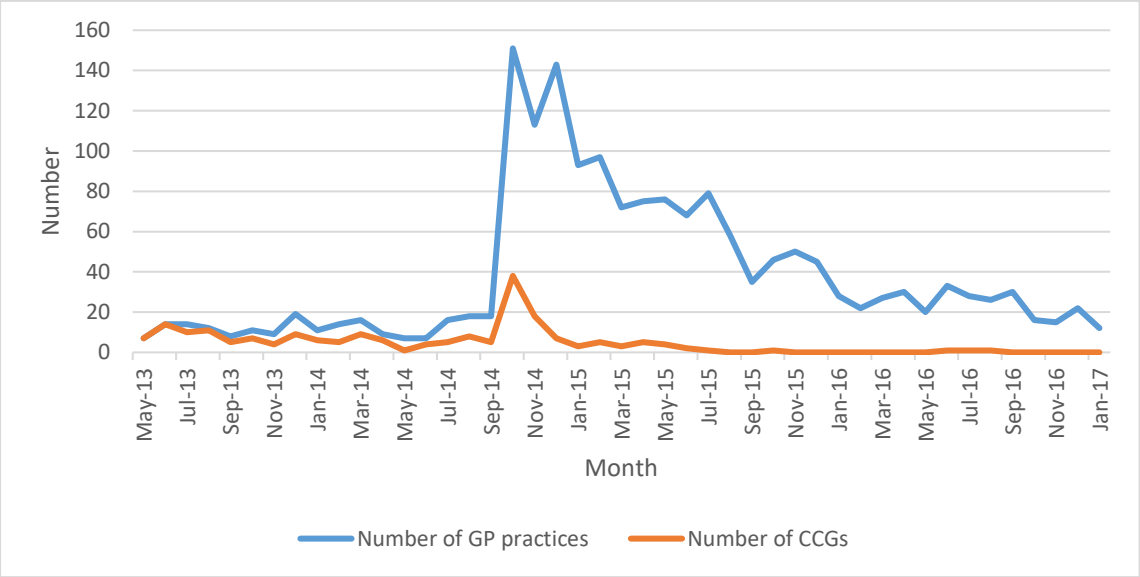
[10] See: https://digital.nhs.uk/services/organisation-data-service/data-downloads/gp-and-gp-practice-related-data

practices and CCGs follows a broadly similar pattern (Figure 3 and Appendix 2, Table 2). The number of new practices prescribing nalmefene for the first time increased considerably in October 2014 (Figure 4).



Source: OpenPrescribing.net, EBM DataLab, University of Oxford, 2017

Figure 3: Monthly nalmefene prescribing by standard GP practices – number of items prescribed, number of practices prescribing, and number of CCGs prescribing (England)



Source: OpenPrescribing.net, EBM DataLab, University of Oxford, 2017

Figure 4: Initiation of nalmefene prescribing by standard GP practices and CCGs (England)

During this period, 1666 GP practices prescribed an item of nalmefene at least once, equating to approximately 22% of GP practices in England.[11] Practices had low levels of prescribing; most had prescribed ten or less nalmefene prescriptions across the whole time period (Table 11). Similarly, although nalmefene had been prescribed at least once in all 206 CCG areas in England, the number of items prescribed was low for most (Table 11). Prescribing levels varied by CCG area, with Wiltshire being the highest prescriber during this time period, although this relatively high number was driven by prescribing by 'non-standard' or specialist prescribers in this area (Appendix 2 Table 3).

Table 11: Extent of nalmefene prescribing by GP practices and CCG areas (May 2013 to Jan 2017)

Number of items prescribed in total	% of practices prescribing at this level	% of CCGs prescribing at this level
1 to 10 items	92.3	29.1
11-50 items	7.0	51.5
51-100 items	0.7	11.7
>100 items	0.0	7.8
Base	1666	206

Source: OpenPrescribing.net, EBM DataLab, University of Oxford, 2017

Although they make up only 5% of the prescribers in the dataset, the 'non-standard' practices (or 'specialist' prescribers) accounted for 19% of the nalmefene prescriptions issued (Table 12). However, as noted earlier, prescribing by such specialist prescribers is unlikely to be fully represented in this data.

Table 12: Prescribing levels by type of practice

Practice type	Number of individual practices in dataset (%)	Number of nalmefene prescriptions issued (%)
Standard GP practices	1666 (95)	7062 (81)
Non-standard practices[1]	90 (5)	1621 (19)
All	1756 (100)	8683 (100)

Source: OpenPrescribing.net, EBM DataLab, University of Oxford, 2017
1.Non-standard practices include Public Health Service (*n*=64), Community Health Service (*n*=15) and Other services (*n*=11)

[11] Estimated using the June 2017 figure for number of GP practices in England from NHS Digital – see: Numbers of Patients Registered at a GP Practice - June 2017 - NHS Digital.

5.3 Impact of the NICE Technology Appraisal (TA) on national prescribing levels

5.3.1 Aim

A significant increase in monthly prescribing of nalmefene occurred in October 2014 (Figure 3), coinciding with the publication of the NICE TA on nalmefene (NICE, 2014a). NICE TAs provide recommendations on the use of treatments or medicines in the NHS, based on a review of their evidence and cost-effectiveness. Where a treatment or medicine is 'recommended' in a TA, there is an obligation on the NHS authorites in England to fund it, usually within three months (NICE, 2018). This is distinct from NICE 'Clinical Guidelines', which provide recommendations on the appropriate NHS treatment for people with specific health conditions, and are advisory rather than mandatory (NICE, 2012). This analysis aims to explore the relationship between the NICE TA publication and nalmefene prescribing levels.

5.3.2 Methods

5.3.2.1 Data source

Data from OpenPrescribing.net on monthly nalmefene items prescribed by all GP practices in England between May 2013 to January 2017 were obtained (Section 5.2.2). The data consisted of 45 time points (or months), 17 of them occurring before the release of the NICE TA, and 28 occurring subsequent to this.

5.3.2.2 Data management

A variable indicating 'intervention' was derived to segment the data into monthly prescribing done before the NICE TA publication and monthly prescribing which occurred at the time of the TA publication and thereafter (see Appendix 2, Table 4).

The original data included a prescribing item value for practices only in months when a prescription occurred. For the Poisson model, the dataset was managed so that individual practice-level prescribing could be taken into account. Zero values were added to ensure that all 1756 practices had a prescribing item value for every month.

5.3.2.3 Data analysis

A time series analysis was conducted using STATA v15 (StataCorp, 2017).

Interrupted time series (ITS) analysis

An ITS analysis was used to model the impact of the NICE TA on nalmefene prescribing by GP practices in England. This approach is useful when exploring the impact of interventions in cases where clinical trials are not possible, for example, in relation to 'natural experiments' such as policy changes (Kontopantelis et al., 2015a). It has been used to evaluate the impact of certain interventions or policies on medications use (Wagner et al., 2002; Jandoc et al., 2015). Segmented regression analysis was employed, which allows a statistical assessment of how much an 'intervention' or 'event' has changed the outcome of interest (Ansari et al., 2003).

The 'intervention' in this analysis is the publication of the NICE draft TA on nalmefene on 2nd October 2014. The outcome of interest is the monthly number of nalmefene items prescribed. The time series was divided into two segments (one for the 'pre-intervention' time period, consisting of the 17 months between May 2013 and September 2014 and one for the 'post-intervention' time period, consisting of the 28 months between October 2014 and January 2017). A regression model was run for each segment separately followed by a combined model to assess the statistical significance of changes in the level and slope of the regression lines pre- and post-intervention. The hypothesised impact model for the intervention is that the effect would be an immediate step change in level of prescribing and an immediate change in slope of prescribing over time (Lopez Bernal et al., 2018).

Two separate models were constructed:

- Model A is a simple linear regression to explore the impact of the TA on total monthly prescribing across all standard GP practices. This model estimated the effect of the TA on national level monthly prescribing.

- Model B uses a mixed effects Poisson model to estimate the effect of the TA on prescribing by all practices in the dataset ('standard' and 'non-standard'). This model includes a fixed effect of practice type ('standard' versus 'non-standard') and it accounts for repeated measures by individual practice (using a random effect of 'practice'). Poisson models are appropriate for count data (used in this analysis), which tend to follow a Poisson rather than a normal distribution (Cameron and Trivedi, 1998) and mixed effects models accommodate the non-independence of repeated measures of practice-level prescribing (Singer and Willett, 2009).

Checking model assumptions

It is important to check the suitability of data for time series analysis (Jandoc et al., 2015; Pickup, 2015; Lopez Bernal et al., 2017). Two issues include autocorrelation and seasonality, which, if present in the data, can confound the results. The longitudinal nature of time series data means that observations across different time points may not always be independent of each other. For example, data collected close together in time are more alike than data which are further apart (Pickup, 2015) – this demonstrates that there is 'autocorrelation' in the data. Correcting for autocorrelation is done to avoid underestimating standard errors and overestimating the significance of an intervention effect in an ordinary least squares regression (Wagner et al., 2002).

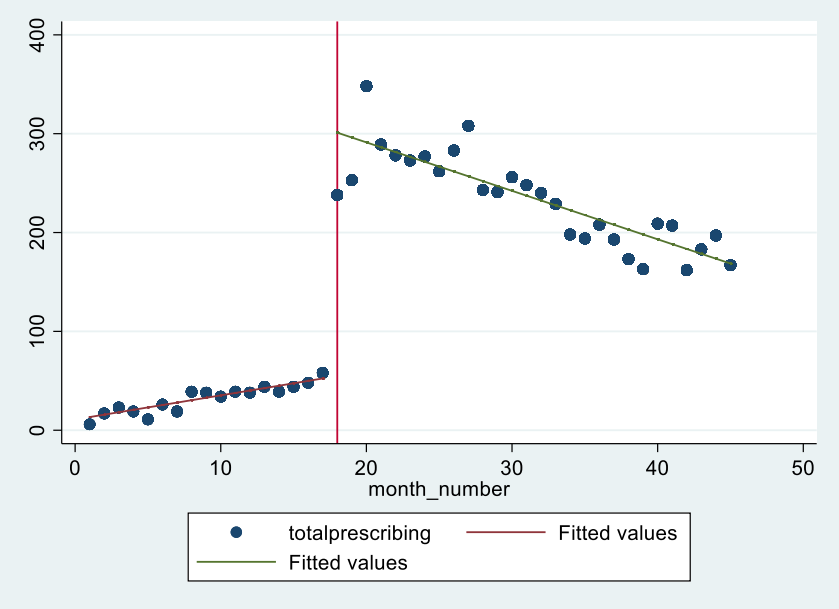
The Durbin alternative test (for small samples) (Durbin, 1970) was used to test for serial autocorrelation of the error terms in each of the segmented regression models. If autocorrelation is detected (for example, this would mean that prescribing for a particular month was correlated with prescribing in the previous month), then this should be addressed in the regression model by including the previous month's prescribing as a predictor variable (known as a 'lagged dependent variable') (Pickup, 2015). The null hypothesis being tested by the Durbinalt test is that there is no serial correlation in the data. The test statistics obtained for both the pre- and post-intervention data (p=0.6977 and p=0.4438, respectively) suggest that the null hypothesis cannot be rejected, and that the data are not serially correlated (Appendix 2, Table 5).

Time series data can show seasonal patterns, which may be independent of any intervention. For example, observations for one month may be more similar to observations in that same month in a different year, than to other months in the year (Wagner et al., 2002). The use of certain medications can vary by season due to seasonal variations in the conditions they are prescribed for (Wagner et al., 2002). A visual inspection of the overall prescribing trend for nalmefene prescribing does not appear to suggest a general seasonal pattern (although there were some increases in items prescribed between November and December in both 2013 and 2014). No statistical tests for seasonality were conducted on this data due to the small number of time points available. This is discussed further in the limitations for this study (Section 5.5.3).

5.3.3 Results

Model A: Simple linear regression model of the impact of the NICE TA on prescribing by 'standard' GP practices

The model suggests that, before the TA release, there were significant month-on-month increases in total nalmefene prescribing by standard general practices in England (an increase of 2.6 items per month on average; $p<0.001$; 95% CI 2.0: 3.2). Following a large increase at the point of the TA release (October 2014), month-on-month total prescribing then decreased significantly (by 4.8 items per month on average; $p<0.001$; 95% CI -6.1: -3.6). Overall, the NICE TA launch was associated with a significant increase in the level of prescribing (an increase of 242.6 items; $p<0.001$; 95% CI: 215.9: 269.3) (Figure 5 and Appendix 2, Table 6). The vertical line in the chart indicates the intervention (the publication of the NICE TA in October 2014 or month 18 in the time series data); the dots represent monthly nalmefene items prescribed by all standard GP practices in England; and the regression lines based on the model are presented for the pre- and post-intervention periods.



Source: OpenPrescribing.net, EBM DataLab, University of Oxford, 2017

Figure 5: Segmented linear regression model of monthly nalmefene prescribing by standard GP practices (May 2013–Jan 2017)

Model B: Mixed poisson model of the impact of the NICE TA on prescribing by all practices in the dataset ('standard' and 'non-standard')

The impact of the NICE TA on monthly prescribing at practice level ('standard' and 'non-standard') was modelled. The model accounts for variation in average prescribing by type of practice ('standard' versus 'non-standard') through inclusion of a fixed effect for practice

type and variation by individual practices by using a random effect for practice. The model suggests that, before the introduction of the NICE TA, the number of nalmefene items prescribed by practices was increasing at a rate of 9% per month (Incident Rate Ratio (IRR)=1.09; $p> 0.001$; 95% CI 1.07:1.11). The NICE guidance was associated with a shift in the level of prescribing – the mean number of items prescribed is 29 times higher after the publication of the TA (IRR=29.1; $p< 0.001$; 95% CI 23.3: 36.5). However, after the immediate increase in prescribing following the TA, the rate of prescribing started to decline over time. Every month after the TA was published the rate of prescribing per practice decreased by 10% (IRR=0.90; $p< 0.001$; 95% CI 0.89:0.92). In summary, the rate of prescribing was gradually increasing before the TA was published. The TA was associated with an immediate large increase in prescribing rates but prescribing rates then declined over the following months. Finally, the model tells us that standard GP practices on average across the whole period prescribe approximately 70% fewer items per month than 'non-standard' practices (IRR=0.30; $p< 0.001$; 95% CI 0.25:0.38) (Appendix 2, Table 7).

5.4 How have GPs used nalmefene for individual patients?

5.4.1 Aim

This analysis aims to understand how GPs have prescribed nalmefene to individual patients. Specifically, it aims to answer the following questions:

- Which patients have been given nalmefene?
- How has the drug been prescribed to these patients?

5.4.2 Methods

5.4.2.1 Data source

Patient-level data were obtained from the Clinical Practice Research Datalink (CPRD), which provides anonymised primary care records for public health research.[12] It collects data from a random sample of around 670 consenting GP practices across the UK (representing approximately 7% of the UK population); the patients included are broadly representative of the UK general population on age, sex and ethnicity and the data are highly validated and

[12] See: https://www.cprd.com/home/

quality assured (Herrett et al., 2015). It includes data on patient diagnoses, treatments, tests, prescriptions and referrals. CPRD data have been used to explore prescribing of a wide range of medications.[13]

5.4.2.2 Participants

Eligible participants were identified from the CPRD Therapy file which holds prescription data. Data on all patients who received a first prescription for nalmefene between 1st May 2013 and 30th June 2017 (*n*=261) were extracted by the team at CPRD.

5.4.2.3 Data management and analysis

Patient data files were provided by CPRD in 'text' format. Those used for this analysis are listed in Appendix 2, Table 8. The files contained coded data for each patient, most of these in 'long' format, where one patient can have multiple rows of data. CPRD codelists and lookup files were provided so that data could be decoded. Much of the data were in the form of medical Read codes (Chisholm, 1990), which are used by GPs to record information about a patient in their IT system, including symptoms, diagnoses, referrals, prescribed medications and test results (Springate et al., 2014). A unique patient identifier code was present in each of the patient files, allowing information about a patient to be linked and collated. The following data management tasks were undertaken:

- Data files were converted from text to Excel format.
- Coded data were decoded using the CPRD 'look up' files documentation.
- Patient-level analysis datasets were created so that key data for each patient could be viewed in one file, with one unique row per patient. Data held across different files were linked and collated using the unique CPRD patient ID number.
- Analysis variables were defined. Patient files were scanned for key data items needed to derive a variable. These data items were collated into a patient-level analysis dataset so

[13] See CRPD-based publications see: https://www.cprd.com/bibliography

that analysis variables could then be constructed. The Python PANDAS[14] data analysis library was used to facilitate the construction of more complex variables, which would have taken longer to construct in Excel. This included scanning data files for specific types of patient data under multiple conditions, for example, to identify and extract the latest recorded weekly alcohol units for each patient before the date of their first nalmefene prescription (see example code for this in Appendix 2 Box 1). The analysis variables derived are described in Table 13.

A descriptive analysis of the data for patients prescribed with nalmefene was then conducted.

Table 13: Key analysis variables

Variable	Description
Age	As patient date of birth was not provided, a proxy measure of age was constructed based on patient year of birth (taken from the 'Patient' file) and current year of analysis (2017).
Alcohol dependence diagnosis	A patient was identified as having an alcohol dependence diagnosis based on the presence of one of a set of Read codes in their 'Clinical' file. Read codes for alcohol dependence were based on those identified in a previous CPRD study (Thompson et al., 2017). The final list comprises 39 codes (Appendix 2, Table 9).
Harmful drinking	The 'Clinical' file was also scanned for the presence of alcohol consumption Read codes indicative of drinking at harmful levels. Patients were identified as drinking at harmful levels based on the presence of at least one of these codes (Appendix 2, Table 10).
Weekly unit consumption of alcohol	Data on each patient's weekly unit alcohol consumption were extracted from their 'Additional Clinical Details' file. As this could be recorded on more than one occasion for many patients, the latest units recorded prior to receiving their first nalmefene prescription were extracted to provide a more recent account of weekly alcohol consumption.
WHO Drinking Risk Level (DRL)	Patients were grouped into a DRL based on their latest recorded weekly units. The proportion drinking at a 'high or very high' DRL (>50 units per week in men and >35 units per week in women) was calculated. A sensitivity analysis was conducted to calculate this proportion based on only those patients with 'recent' (recorded in the 12 months prior to nalmefene) consumption data. Both figures are reported.
Nalmefene prescription details	Data on prescriptions were extracted from the patient 'Therapy' file. Variables were derived for the total number of prescriptions and the total quantity of tablets prescribed to each patient. For patients with more than one nalmefene prescription (n=95), a crude measure of 'duration' of prescribing was calculated using the time difference (number of days) between their first and last recorded nalmefene prescription. For these patients, a usage rate was also estimated based on the total quantity of tablets prescribed up until the point of their last recorded prescription (i.e. not including the quantity given for this last prescription) over the duration period (number of days).

[14] This is an open source data analysis and manipulation tool which uses the Python programming language. See: https://pandas.pydata.org/.

Adjunct psychosocial support	Patients were identified as having received psychosocial support for their alcohol problems based on the presence of one of a set of 24 medical Read codes developed in a previously published CPRD study (Thompson et al., 2017). The dates on which these Read codes were recorded were used to define psychosocial support relating to the patient's nalmefene treatment. (See Appendix 2, Table 11 for a list of Read codes used)
Previous treatment for alcohol problems	Data from the patient 'Therapy' and 'Clinical' files were scanned for information indicating treatment for alcohol problems prior to receiving nalmefene. Previous treatment is defined by presence of one of the following criteria prior to the date of the first nalmefene prescription: • Receipt of a prescription for another approved alcohol dependence drug (disulfiram, acamprosate, or naltrexone) or a drug used 'off-label' to treat alcohol problems (topiramate or baclofen). (Appendix 2, Table 12 lists product names and codes) • Receipt of a prescription for chlordiazepoxide, a drug used for managed withdrawal from alcohol. (Appendix 2, Table 12 lists product names and codes) • Presence of a medical Read code indicating alcohol detoxification treatment (Appendix 2, Table 13). • Presence of a medical Read code relating to a psychological intervention for alcohol problems (Appendix 2, Table 11 lists codes).
Patients 'newly presenting' to their GP for alcohol problems	The patient 'Therapy' and 'Clinical' files were scanned for data indicating whether a patient had previously engaged with their GP for alcohol problems (either they had received alcohol treatment or that an alcohol problem was recorded in their record). Patients were identified as 'newly presenting' if they met the following criteria (based on information recorded before their first nalmefene prescription, but excluding the last 30 days to avoid recorded data that may relate to their nalmefene assessment): • No medical Read codes for alcohol dependence • No medical Read codes indicating harmful drinking • No medical Read codes for psychosocial support relating to alcohol problems • No medical Read codes for liver problems relating to alcohol • No medical Read codes relating to alcohol detoxification • No prescription for alcohol dependence drugs or chlordiazepoxide
Comorbid health conditions	Receipt of prescriptions for selected medications prior to receiving nalmefene was used as a proxy for comorbid health conditions relating to alcohol. The medications selected were those which can be prescribed for depression, anxiety and gastrointestinal disorders, conditions associated with excessive drinking (Mannelli and Pae, 2007; Flensborg-Madsen et al., 2009; Fein, 2015). Medical Read codes indicating alcohol-related liver problems were also examined. These were defined as follows: • Receipt of an SSRI Anti-depressant (fluoxetine, paroxetine, citalopram, dapozetine, escitalopram, fluvoxamine or sertraline) • Receipt of diazepam • Receipt of an anti-ulcer drug (ranitidine, omeprazole, esomeprazole, pantoprazole or lansoprazole) • Presence of a medical Read code indicating alcohol-related liver problems (See Appendix 2, Tables 14 and 15 for Read codes included)
Level of GP contact	The patient 'Consultation' file was scanned to identify patient contact with their GP in the 12 months prior to receiving nalmefene. In CPRD data a patient may have multiple entries within their patient record, however, not all represent a face-to-face consultation with their GP, and multiple 'events' in the consultation file can be

	recorded within one single consultation (Herrett et al., 2015). For each patient the number of consultations was calculated by counting each unique event date entered. Where multiple entries were recorded under the same date, this was counted as one consultation, an approach taken in other CPRD studies (Otete et al., 2015). Consultations data have been grouped into types, based on the definitions used in a published CPRD study (Kontopantelis et al., 2015b). They include: • any consultation (which could include administrative tasks); • face-to-face or telephone consultations with any staff member; • face-to-face or telephone consultations with a GP or Practice Nurse; • and face-to-face or telephone consultations with a GP. (See Appendix 2, Table 16 for definitions used for consultation type)
Pre-nalmefene assessment and subsequent follow up	A pre-nalmefene assessment was defined as a face-to-face or telephone consultation with any staff member which was dated 2-4 weeks before the date of the patient's first nalmefene prescription. Follow-up assessments were defined as face-to-face or telephone consultations by any staff member in the first one and two months from the date of the first nalmefene prescription.

5.4.2.4 Ethical considerations

The patient-level anonymised CPRD data is drawn from GP practices who have agreed to be part of the database. Information for members of the public is available on the CPRD website about the use of medical records in research, including confidentiality and how they can opt out if they do not wish their medical records to be used.

A key ethical consideration is the extent to which an individual can be identified from any analysis of this data. The sample of patient data obtained from CPRD is completely anonymised and presented at a geographical level that would not risk disclosing the identity of any patients (the data are provided at regional level only). Attempts to identify patients, practices or clinicians are specifically prohibited when using CPRD data, and in this study care was taken to maintain the anonymity of the data when reporting results. All data were stored on the University of Stirling's secure servers, and were only accessible by my supervisors and me.

The study protocol for this analysis was approved by the CPRD Independent Scientific Advisory Committee (ISAC) in June 2017 (Protocol 17_120R). Ethics approval to analyse the CPRD data was also granted by the University of Stirling NHS Invasive or Clinical Research (NICR) Committee in June 2017 (NICR 16/17 – Paper No.71).

5.4.3 Results

The following results are based on a descriptive analysis of the data, and are presented in two sections. Section 1 describes the characteristics of the 261 nalmefene patients (their age, gender, alcohol diagnoses and drinking behaviour, previous alcohol treatment, comorbidity and GP contact). Section 2 describes how nalmefene has been prescribed to these patients (the number of prescriptions received, the quantity and duration of prescribing, rate of usage, receipt of psychosocial support, and receipt of pre- and post-nalmefene assessments).

5.4.3.1 Results Section 1: Characteristics of nalmefene patients

Age and sex

Most nalmefene patients (80%) were between 35 and 64 years of age. The average age for both male and female patients was 50.3 years (95% CI 48.6:51.4). Broadly similar age distributions were found for male and female patients. The sample comprised more males than females (58% compared with 42%) (Figure 6).

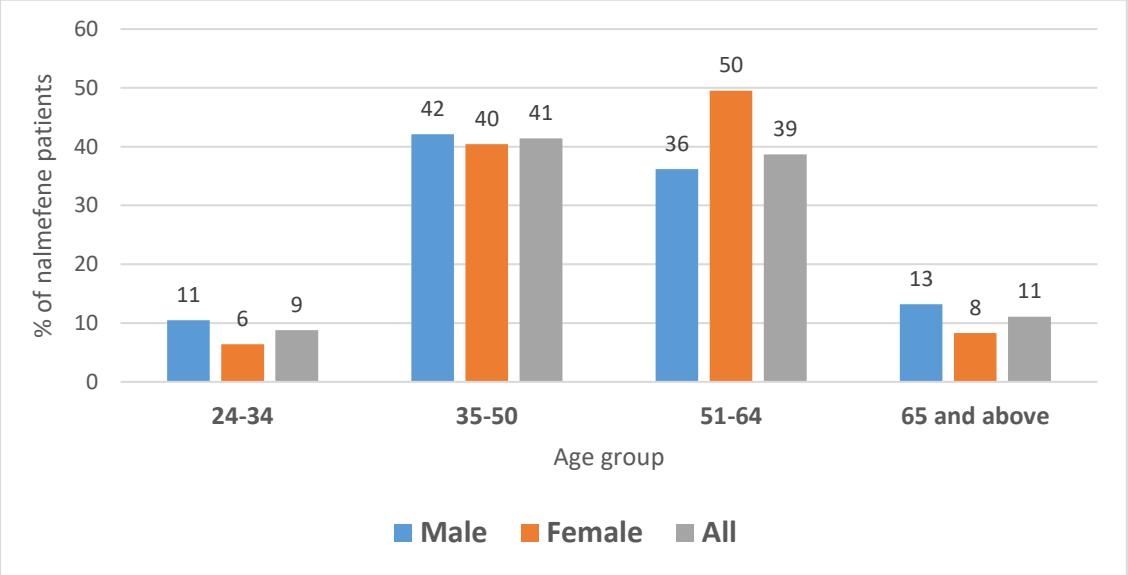


Figure 6: Age and sex profile of nalmefene patients

Alcohol dependence and harmful drinking

Nalmefene was licensed for patients with alcohol dependence. Read codes indicating an alcohol dependence diagnosis were recorded for 43% of nalmefene patients prior to their first nalmefene prescription. An additional third (32%) had a Read code indicating harmful drinking, and a quarter of patients (25%) had no recorded Read code indicating either alcohol dependence or harmful drinking (Table 14 and Appendix 2 Tables 9 and 10).

Table 14: Alcohol Read codes recorded for nalmefene patients prior to first nalmefene prescription

Alcohol Read codes	Number of patients	% of all nalmefene patients
Any Read code indicating alcohol dependence OR harmful drinking recorded pre-nalmefene	196	75
- Any alcohol dependence Read code pre-nalmefene	(113)	(43)
- Any harmful drinking Read code only (no Alcohol dependence Read code present) pre-nalmefene	(83)	(32)
No Read codes for either alcohol dependence or harmful drinking recorded pre-nalmefene	65	25
All	261	100

Weekly unit consumption of alcohol

Nalmefene was licensed for patients drinking at high DRLs. Latest recorded weekly unit consumption data before receiving nalmefene[15] enabled patients to be classified into DRL groups. It suggests that 35% of patients (32% of males and 39% of females) were drinking at a 'high or very high' DRL (>50 units per week in men and >35 units per week in women); 18% had no unit consumption data recorded at all; and 5% had a recording of zero units (Figure 7). The proportion drinking above the recommended weekly guideline of 14 units was 59%. Consumption data for two thirds of nalmefene patients were recorded a long time before their first prescription was made. Restricting the analysis to patients with more recent consumption data (recorded in the 12 months prior to receiving nalmefene), suggests that 63% of all patients were drinking at a 'high or very high' DRL (although this is based on around a third of nalmefene patients; *n*=83).

[15] Note that the dates of patients' latest recorded weekly alcohol units prior to nalmefene varied widely: for 32% of patients, this was recorded within the 12 month period before nalmefene; for 29% of patients this was recorded 1 to 5 years before nalmefene; and for 21% of patients this was recorded more than 5 years prior to nalmefene.

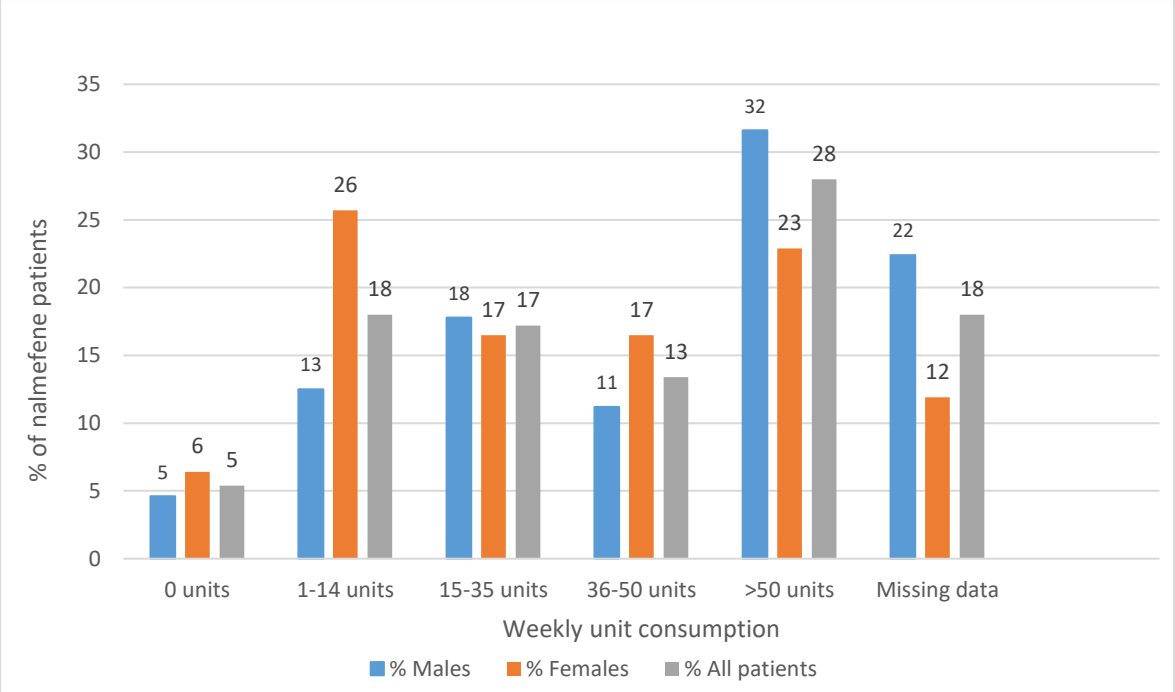


Figure 7: Latest recorded weekly alcohol unit consumption among all nalmefene patients (prior to nalmefene)

Previous treatment for alcohol problems

Altogether, one in two nalmefene patients (50%) had received another alcohol treatment prior to receiving nalmefene (an alcohol dependence drug, a withdrawal drug, alcohol detoxification or a psychological intervention relating to alcohol). Of the other 50%, with no prior alcohol treatment recorded, two-thirds (65%; or 33% of all nalmefene patients) had data in their records suggesting they had previously engaged with their GP for an alcohol problem at some point prior to receiving nalmefene, but had no recorded treatment in their records. The remaining third (35%; or 17% of all nalmefene patients) had no data recorded which indicated an existing alcohol problem (including treatment) at any stage prior to nalmefene[16] (Figure 8). However, they had a relatively high level of GP contact in the year prior to receiving nalmefene (a mean rate of 6.9 face-to-face or telephone consultations with the GP or practice nurse; 95% CI 5.3:8.5) and a large proportion (60%) had been prescribed a

[16] An alcohol problem is defined as any data suggesting an individual has a problem with alcohol (medical Read codes for alcohol dependence, harmful drinking, alcohol-related liver problems, alcohol detoxification) or receipt of alcohol treatment (including pharmacological or psychological interventions). Data recorded in the 30 days immediately before a first nalmefene prescription were excluded to distinguish it from data relating to their nalmefene assessment.

medication commonly used to treat problems relating to alcohol use (an SSRI, anti-ulcer drug or diazepam).

Almost a third of nalmefene patients (29.9%) had been prescribed one other drug potentially for alcohol dependence prior to receiving nalmefene, suggesting that, for the majority of nalmefene patients (70.1%), their first alcohol dependence prescription was nalmefene. The most commonly prescribed alcohol dependence drug given to nalmefene patients was acamprosate (received by 25% prior to nalmefene); the prescribing of other alcohol dependence drugs was lower (disulfiram 5%; naltrexone 3%; baclofen 3%; topiramate 1%) Almost one in four nalmefene patients (24%) had previously received chlordiazepoxide, which is commonly prescribed to treat problems associated with withdrawal from alcohol (Appendix 2, Table 17). Read codes indicating receipt of a psychosocial intervention for alcohol were present for 23% of nalmefene patients, whilst those for alcohol detoxification were present for 13% (Figure 9 and Appendix 2, Tables 11 and 13).

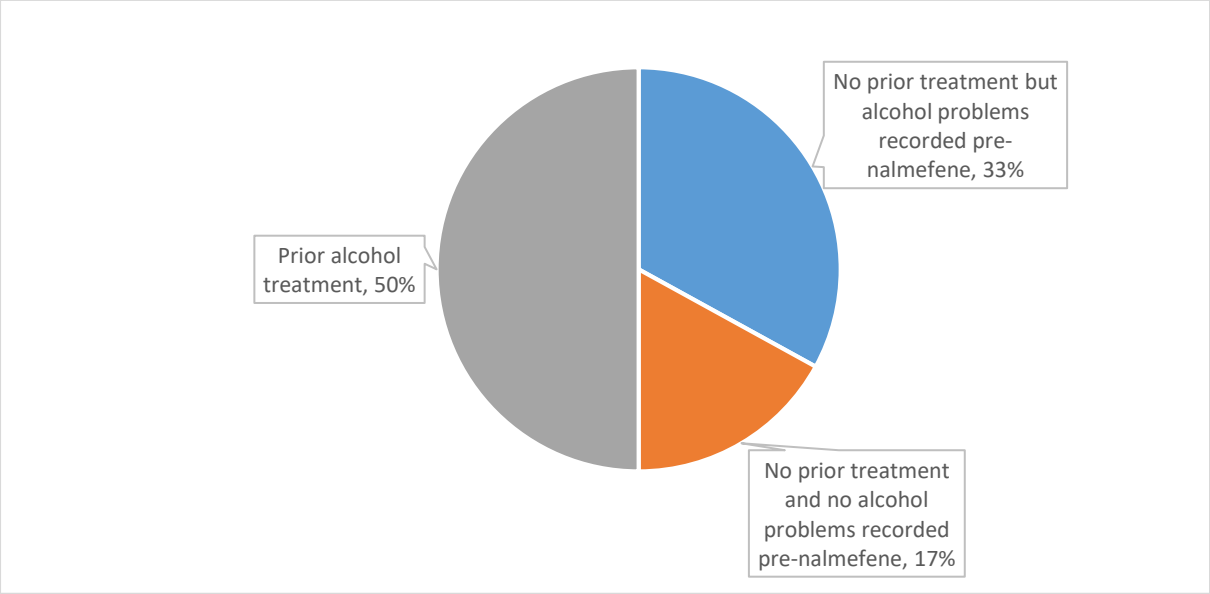
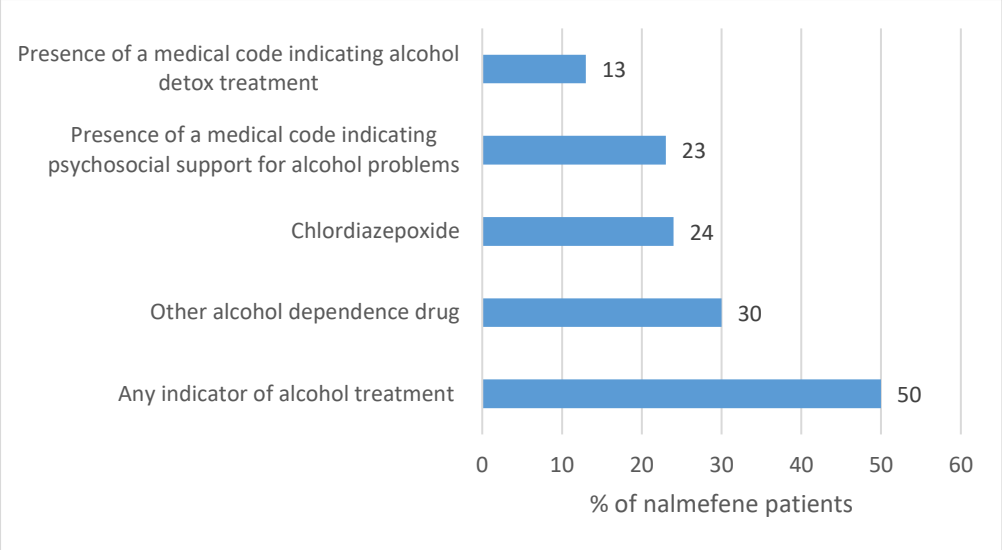


Figure 8: Nalmefene patients according to prior treatment status and alcohol problems recorded pre-nalmefene



Note: Other alcohol dependence drugs are: disulfiram, acamprosate, naltrexone, baclofen and topiramate.

Figure 9: Alcohol treatment recorded prior to nalmefene

Cormorbidity and levels of GP contact among nalmefene patients

The health of patients who received nalmefene was examined using previous prescriptions for medications indicating more complex health or alcohol-related problems, data on the level of previous GP contact and medical Read codes indicating liver problems.

A large majority of nalmefene patients (74%) had been prescribed an SSRI anti-depressant prior to receiving nalmefene; 58% had been prescribed an anti-ulcer drug; and 47% diazepam (commonly used to treat a range of conditions including anxiety and alcohol withdrawal syndrome (Weintraub, 2017)). A high proportion of all patients who had been prescribed nalmefene had been prescribed these drugs in the 12 months prior to their first nalmefene prescription, and some had prescriptions dated within the three months preceding their nalmefene. Around 28% of patients who had been prescribed nalmefene had received all three of these drug types at some point before receiving nalmefene (Table 15).

Table 15: Receipt of SSRI, anti-ulcer drugs, and diazepam prior to nalmefene

Drug	% of patients received drug pre-nalmefene	% of patients received drug 12 months pre-nalmefene	% of patients received drug 3 months pre-nalmefene
SSRI Anti-depressants[1]	73.9	48.7	37.5
Anti-ulcer drugs[2]	57.9	35.6	30.7
Diazepam	47.1	21.1	11.1
Any one of these drug types	88.8	69.7	59.4
All three of these drugs types	27.9	6.9	0.0
Base	261	261	261

1. SSRI drugs: fluoxetine, paroxetine, citalopram, dapozetine, escitalopram, fluvoxamine or sertraline.
2. Anti-ulcer drugs: ranitidine, omeprazole, esomeprazole, pantoprazole, lansoprazole.

Scanning records for Read codes relating to alcohol-related liver problems resulted in 6% of the nalmefene patients with at least one of these codes entered in their records before the date of their first nalmefene prescription (See Appendix 2, Table 15 for the Read codes used).

Almost all patients who had been prescribed nalmefene had received a primary care consultation of some type in the 12 months prior to receiving nalmefene (see Appendix 2, Table 16 for consultation type groupings).[17] Direct consultations (face-to-face or telephone) delivered by a GP or Practice Nurse (see Appendix 2, Table 18 for a list of staff included) were received by 93% of patients. A large proportion (58%) had received six or more contacts of this type in the 12 months prior to nalmefene, the average being 7.7 contacts across the group as a whole (Table 16 and Table 17).

There was no significant change in patients' contact rates pre- and post-nalmefene. A paired sample *t*-test was used to check whether the extent of the increases/decreases in contact rate were significant on average. The result was not significant, indicating no difference in level of GP contact pre- and post-nalmefene treatment (t=1.08, df=210 p=0.296) (see Appendix 2 Table 19).

[17] Note that consultations dated within the 30 days immediately before the nalmefene prescription date have been excluded, as it is possible that some of these may have been part of the pre-assessment for nalmefene.

Table 16: Primary care consultations in the 12 months prior to first nalmefene prescription[1] and 12 months after the last nalmefene prescription

Type of consultation	% of patients who received a consultation	
	12 months before first nalmefene prescription	12 months after last nalmefene prescription
Any consultation type	99.2	99.1
Direct (face-to-face or tel) consultation with any staff	95.0	91.0
Direct consultation with GP or Practice Nurse	93.5	91.0
Direct consultation with GP	92.7	86.3
Base	261	211[2]

1. Excludes consultations dated in the 30 day period prior to the nalmefene prescription to avoid any which may have related to an assessment for nalmefene.
2. The analysis is based on fewer patients (*n*=211) as it had to be limited to those who had at least 12 months data on consultations after their last nalmefene prescription.

Table 17: Direct primary care consultations (face-to-face or telephone) with a GP or practice nurse in the 12 months prior to first nalmefene prescription[1] and 12 months after the last nalmefene prescription

Number of consultations in the 12 month period	% of nalmefene patients who received a consultation	
Frequencies	12 months before first nalmefene prescription	12 months after last nalmefene prescription
1 to 3	20.7	24.2
4 to 5	14.9	11.8
6 to 11	35.6	32.2
12 to 19	18.4	16.1
20 or more	3.8	6.6
None/other type	6.5	9.0
Base	261	211[2]
Mean direct consultations with any staff	9.1 (95% CI 8.2:10.0)	9.6 (95% CI 8.2:11
Mean direct consultations with GP or PN	7.7 (95% CI 7.0:8.4)	7.8 (95% CI 6.8:7.8
Mean direct consultations with GP	6.8 (95% CI 6.1:7.5)	6.7 (95% CI 5.8:7.6)

1. Excludes consultations dated in the 30 day period prior to the nalmefene prescription to avoid any which may have related to an assessment for nalmefene.
2. The analysis is based on fewer patients (*n*=211) as it had to be limited to those who had at least 12 months data on consultations after their last nalmefene prescription.

5.4.3.2 Results Section 2: How nalmefene has been prescribed to patients

A total of 603 nalmefene prescriptions were issued to the sample of 261 patients between May 2013 and June 2017. The overall number of prescriptions increased gradually from mid-2013 to peak in Oct-Dec 2014 (Figure 10), a pattern similar to the monthly prescribing by all GP practices in England (see Figure 3).

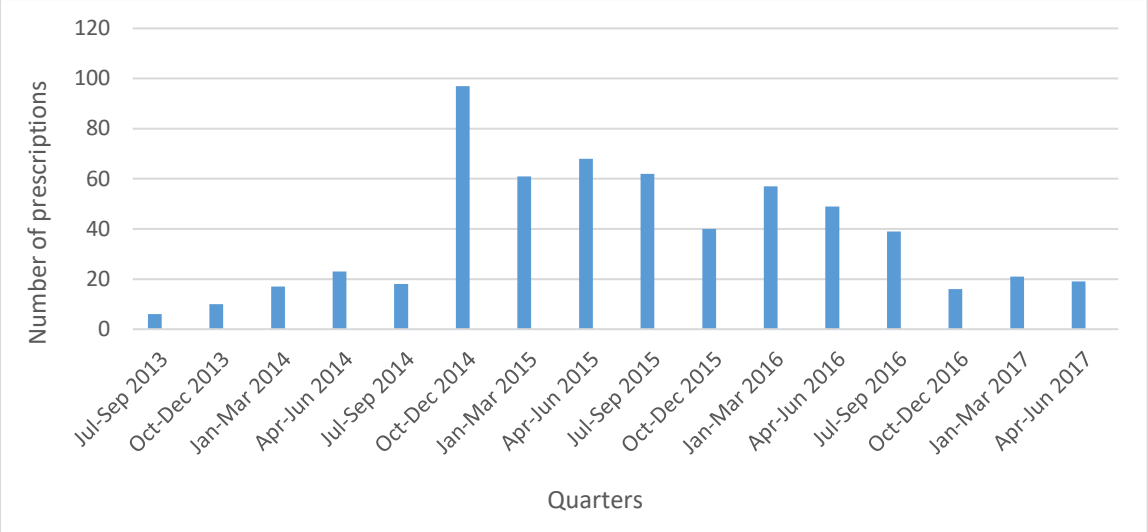


Figure 10: Number of nalmefene prescriptions per quarter (July 2013 to June 2017)

Number of prescriptions received per patient

The number of nalmefene prescriptions received by each patient ranged widely, from 1 to 39, although most (64%) received only one. Around 8% of patients (*n*=20) had received six or more prescriptions during the study period, accounting for 37% of all nalmefene prescriptions (Table 18).

Table 18: Number of nalmefene prescriptions

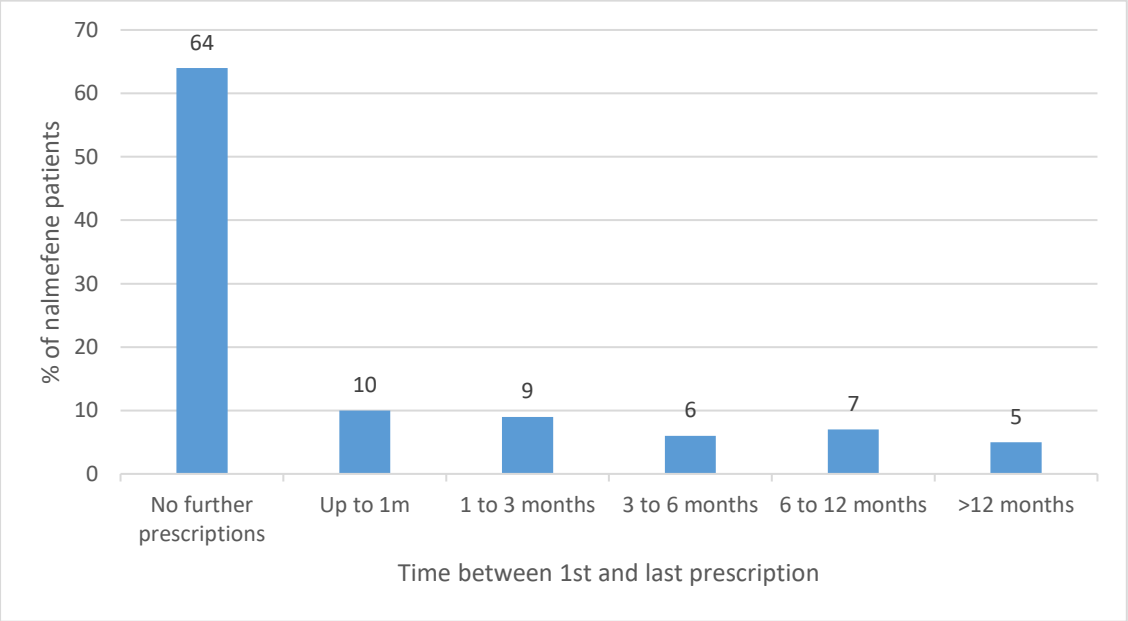
Number of prescriptions[1]	Number of patients	% of patients	Number of prescriptions	% of total prescriptions
One	166	63.6	166	27.5
Two	36	13.8	72	11.9
Three to five	39	14.9	143	23.7
Six to nine	12	4.6	111	18.4
Ten or more	8	3.1	111	18.4
All	261	100	6.3	100%

[1] The data include records up until June 2017. It is possible that some patients received subsequent prescriptions after this date, which are not captured in the data. Seven patients had their first prescription between April 2017 and June 2017. When they are removed from this analysis, the proportion of patients with only one prescription remains high at 61%.

Quantity prescribed, duration of prescribing and rates of usage

Nalmefene is licensed to be taken as one tablet per day as needed. The overall quantity of tablets prescribed to individual patients between July 2013 and June 2017 varied widely, from 1 to 756 tablets, although this will depend in part on the length of time a patient has been in the dataset. The quantity of tablets prescribed for a first prescription of nalmefene varied from 1 to 56, but was most commonly 14 tablets (the size of a standard nalmefene pack) (See Appendix 2, Table 20).

An analysis of duration of nalmefene treatment (see Section 5.4.2) suggests that 19% of patients had a last prescription recorded within three months of first receiving the drug; 13% within three to 12 months of first receiving the drug; and a small proportion (5%) more than 12 months on from their first prescription (Figure 11). Although this suggests some patients have been receiving nalmefene over relatively long periods of time, the frequency of nalmefene prescriptions varies widely for these patients (ranging from 2 to 39 prescriptions among the 12 patients still receiving nalmefene a year on from the initial prescription).



Base: all patients who had been prescribed nalmefene (*n*=261)

Figure 11: Duration of nalmefene treatment

Rates of usage of nalmefene tablets were calculated for the 95 patients with more than one nalmefene prescription (see Table 13 in Section 5.4.2). These were relatively high on average, with a mean rate of 0.7, suggesting that nalmefene was being used on around 70% of days. Most patients (62%) had a rate of 0.7 or higher. Rates of usage among the 20 patients who had received six or more nalmefene prescriptions were also high – a mean rate of 0.7 (Appendix 2, Table 21).

Psychosocial and psychological support received by nalmefene patients

To be prescribed nalmefene, a patient must also receive continuous psychosocial support. Around 1 in 3 patients (31%) had a Read code indicating receipt of a psychosocial or psychological intervention relating to alcohol. Narrowing these Read codes to dates close to their first nalmefene prescription suggests that 6.5% of patients have received psychosocial

support within a one-month period either side of their nalmefene prescription (8% had received this within a three-month period either side) (Table 19).

Table 19: Presence of psychosocial support Read codes in nalmefene patient records

Psychosocial Support[1]	**Number**	**% of all nalmefene patients**
Patients who have a Read code for psychosocial support: - recorded at any time	80	30.6
- recorded within a 1 month period either side of their first nalmefene prescription	(17)	(6.5)
- recorded in a 1 – month period either side of their first nalmefene prescription	(4)	(1.5)
- recorded more than 3 months either side of their first nalmefene prescription	(59)	(22.6)
Patients who have no psychosocial support Read codes recorded prior to or after receiving nalmefene	181	69.3
All	261	100

1. See Appendix 2, Table 11 for a list of the medical Read codes used to define psychosocial support.

Pre-nalmefene assessment and subsequent follow up of nalmefene patients

To be prescribed nalmefene, patients should receive an initial assessment followed by another two weeks later to ensure they were still drinking at a high DRL. Two-fifths (40%) of nalmefene patients had received a direct consultation (face-to-face or telephone contact) with a staff member in the two-to-four weeks prior to receiving nalmefene (Appendix 2, Table 22). With regard to follow up consultations after their initial nalmefene prescription, 59% of patients had at least one direct consultation in the month following their initial nalmefene prescription. By two months this figure was 72% (Appendix 2, Table 23).

5.5 Discussion

This section summarises and discusses key findings from the study, drawing on the wider literature on nalmefene and on alcohol treatment. It also outlines the study strengths and limitations.

5.5.1 Uptake and trends in nalmefene use in UK primary care

During the analysis period (May 2013 to January 2017) nalmefene was prescribed at least once by around a quarter of GP practices in England, with most issuing a small number of prescriptions. Prescribing of nalmefene was higher in some CCG areas, although the reason for this is not clear from this analysis. Primary care prescribing for alcohol dependence is low generally (Thompson et al., 2017), but prescribing of nalmefene is even lower, accounting for less than one percent of alcohol-related prescriptions in primary care in England in 2017[18] (NHS Digital, 2018) and in Scotland in 2017/18 (The Scottish Public Health Observatory, 2019).

The time series analysis of trends in prescribing suggest that GPs were influenced by the launch of the NICE TA on nalmefene, at least initially, in line with research on other NICE guidelines (Wathen and Dean, 2004; Curtis et al., 2018). However, prescribing was increasing gradually before the NICE TA release, possibly due to a range of other factors, including earlier drafts of the NICE report (released in July and September), other sources of information or guidance (Jacobson, 1997; Gabbay and le May, 2004), the SMC approval of nalmefene in October 2013, and ongoing positive media coverage and marketing activities undertaken (discussed in Chapters 6 and 7). The general trend in nalmefene prescribing since 2015 has been downward, a trend also observed for other alcohol dependence drugs (NHS Digital, 2018). The potential reasons for the low uptake of nalmefene here are discussed further in Chapter 7.

5.5.2 How nalmefene is prescribed to patients in primary care

Nalmefene use in real-world clinical settings has been evaluated by a small number of Lundbeck-sponsored post-marketing studies; these have either been specifically conducted in the nalmefene licensed patient group (Castera et al., 2019) or have been conducted with a small numer of patients from outside of the UK (Di Nicola et al., 2017; Barrio et al., 2018; Barrio et al., 2019a; Barrio et al., 2019b). Patient-level prescribing data has been used widely to understand how drugs are used in real-world clinical settings (Gama, 2008; Herrett et al.,

[18] Total items prescribed include all acamprosate, disulfiram and nalmefene items prescribed in primary care in England in 2017 – see https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-alcohol/2018/part-3.

2015), and, at the time of writing, this study is the first to examine nalmefene using patient data from UK primary care. The following sections discuss the extent to which nalmefene patients align with the licensing conditions for the drug and the characteristics of the wider RCT population, the extent to which they may be newly engaging with alcohol treatment, and details relating to the nalmefene prescription.

To what extent is nalmefene prescribed in line with its licensing conditions?

Nalmefene is licenced for use in patients with alcohol dependence but without withdrawal symptoms who are drinking at a high DRL (including at 2 weeks after their initial assessment); patients should also receive continuous psychosocial support alongside the drug. This analysis suggests that many patients who have been prescribed nalmefene do not align with the licensing conditions. Less than half (43%) had an alcohol dependence diagnosis recorded; around a third (35%) met the criteria for drinking at a high DRL (65% if based on recently recorded unit consumption data); and a small minority (8%) had received psychosocial support alongside their nalmefene prescription. Less than half (40%) appear to have received a pre-nalmefene assessment (this part of the licensing is important in providing patients with an opportunity to reduce their DRL by themselves over a 2-week period, as occurred in the RCTs). Certain data limitations make it difficult to draw firm conclusions from this data (as discussed in Section 5.5.3). However, lower levels of drinking in real-world patients who had been prescribed nalmefene compared to RCT patients were among the mismatches reported in an observational study of nalmefene (Barrio et al., 2018; Barrio et al., 2019a; Barrio et al., 2019b). The small proportion receiving psychosocial support is also consistent with other research (Thompson et al., 2017) and with anticipated concerns about how nalmefene would be given to patients in primary care (Kerr, 2013).

To what extent do nalmefene patients align with the RCT patient population?

Comparison of patients who had been prescribed nalmefene with those in the Lundbeck-sponsored trials highlighted some similarities and differences on certain characteristics (see Appendix 2, Table 24). The mean age of 50 years is consistent with the RCTs (between 44 and 52) and data on alcohol treatment (Public Health England, 2018). Patients with alcohol problems are often not treated until later, the reasons for which are highly variable between individuals and not fully understood, but may include stigma, lack of services or acceptable services, an unawareness or lack of acceptance of alcohol problems, or because they are not

currently experiencing any health impacts (Cunningham et al., 1993; Clark and Simpson, 2014; Alcohol Research UK, 2018).

Most nalmefene patients were male (58%). The proportion who were female (42%) was higher than in the main nalmefene RCTs (25 to 34%). Females have been under-represented in clinical trials for various reasons (Melloni et al., 2010), including in recent trials of alcohol dependence drugs (Agabio et al., 2016). Although excessive drinking is more common in males, alcohol treatment data suggest a disproportionately higher proportion of females are in treatment than would be expected, given the prevalence of problematic drinking in females (Public Health England, 2018) and in one CPRD study, females were significantly more likely than males to receive an alcohol dependence medication (Thompson et al., 2017). Possible contributory factors include that females may be more willing to engage with and accept treatment when offered (Weisner et al., 2001), or that, due to barriers experienced by females in accessing services, they present to services when their condition is more serious (McCrady, 2020), making them more likely candidates for a pharmacological approach (Thompson et al., 2017).

Patients who had been prescribed nalmefene had high levels of alcohol-related comorbidity and contact with their GP in the year prior to receiving nalmefene. High rates of psychiatric comorbidity were reported in an observational study of nalmefene (Barrio et al., 2019b). RCTs, however, often exclude patients with comorbidities (Persaud and Mamdani, 2006; Hoertel et al., 2014) and this is also true for the nalmefene RCTs (with the exception of the SENSE trial which included a small number of patients with a stable comorbid psychiatric disorder) (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014a). The high comorbidity among patients who had been prescribed nalmefene may partly explain their relatively high GP contact level in the year prior to receiving nalmefene (ranging from 6.8 to 9.1 contacts on average, depending on type of consultation). Other studies have highlighted the high rates of health care contact among patients with alcohol problems (Morris et al., 2012; Otete et al., 2015). Mean yearly contact rates among the general population (some based on CPRD data) are lower, ranging from 3.4 to 5.4 (Hippisley-Cox and Vinogradova, 2009; Kontopantelis et al., 2015b; Hobbs et al., 2016).

Clinical setting and country are other important factors which distinguish the real-world patients who had been prescribed nalmefene from those who participated in the clinical trials. Few patients were recruited into the nalmefene RCTs from primary care settings and few

were from the UK (only the Sense trial recruited from a UK site) (Fitzgerald et al., 2016). This raises questions about the applicability of the nalmefene evidence to the drinking problems of patients presenting to UK primary care.

To what extent are nalmefene patients newly engaging with alcohol treatment or newly presenting to the GP for alcohol problems?

Nalmefene was marketed as a drug with the potential to engage new patients into treatment (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014a). This analysis suggests that one in two patients who had been prescribed nalmefene were engaged in alcohol treatment[19] before receiving nalmefene. By comparison, the main RCTs reported that 22% to 40% of patients had received previous treatment (although it is unclear what the definition of treatment is in this context) (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014a). If half of nalmefene patients had no prior alcohol treatment recorded, this may partly support the claims that nalmefene may encourage a wider group of drinkers into treatment, people who had not previously accessed treatment for their problems. At the least it suggests that GPs have tried nalmefene with a disparate group of patients, some with experience of alcohol treatment and others possibly new to treatment.

Data on alcohol problems recorded prior to receiving nalmefene suggest that just under a fifth (17%) of patients were newly presenting to their GP for alcohol problems (that is, they had no data in their GP records indicating an alcohol problem or alcohol treatment prior to receiving nalmefene). However, the relatively high levels of comorbidity and GP contact recorded prior to receiving nalmefene (including in this 17% of patients) raises questions about whether this group are presenting to the GP for the first time with their alcohol problems or whether data on their alcohol problems has not been fully recorded, issues raised in other research (Otete et al., 2015). It also raises questions about whether GPs are asking patients about alcohol, even though they have issues that are potentially caused or worsened by alcohol. Some of these issues are discussed further in Chapter 7.

[19] This is based on a broad definition of treatment (receipt of a prescription for an alcohol dependence or withdrawal drug; presence of a medical Read code indicating alcohol detoxification treatment; or presence of a Read code for psychosocial support relating to alcohol problems).

How have nalmefene prescriptions been issued to patients?

Most patients received only one nalmefene prescription. Whether they disengaged with nalmefene treatment due to lack of efficacy, side effects, or because they managed to reduce their drinking without the need to take the medication or with a small number of pills, is uncertain from this data. However, research on other pharmacotherapy for alcohol dependence reports similar patterns, with authors suggesting that a lack of support for patients to remain engaged with their treatment may be a factor (Thompson et al., 2017). A small proportion of patients (8%) received six or more prescriptions, which may suggest that, for some patients, the drug has been experienced as helpful. More insights on understanding these prescribing behaviours are discussed in Chapter 7.

A small minority of patients (5%) were still receiving prescriptions more than 12 months on from their initial prescription, which is a longer duration than in the RCTs (6 to 12 months). Patients' experiences of taking nalmefene for longer periods are unknown, and caution is advised about using it continually for longer than 12 months (Lundbeck Ltd., 2013b), and in some local prescribing committees, for longer than six months (Dorset Medicines Advisory Group, 2015; NHS Haringey CCG, 2015). These restrictions are likely driven by safety as well as cost implications, given the relatively higher cost of nalmefene compared with other alcohol dependence medications (NHS Digital, 2018).

The maximum daily dose for nalmefene is one tablet. However, because it can be used 'as-needed', the usage rate[20] will vary across individual patients. This study reports an average usage rate of 70%, which is higher than the rate reported in the RCTs (48 to 57% of study days) (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014a). It is also higher than the estimated usage rates used to model the costs of nalmefene (50%) (Lundbeck Ltd., 2012). Higher usage rates in clinical practice, also reported in the observational study of nalmefene (Barrio et al., 2019b), will have potential cost implications for services.

5.5.3 Strengths and limitations

The strengths and limitations of the data and analytical approaches used are now discussed.

[20] Rate of usage is based on the number of tablets consumed over the number of study days.

OpenPrescribing.net data

These data are based on all GPs in England, providing a complete picture of prescribing at a national level, rather than relying on a sample (Curtis and Goldacre, 2018). However, the data only include prescriptions dispensed by a pharmacist (Curtis et al., 2019) and it is possible that some nalmefene prescriptions may have been issued by GPs to patients but not presented to a pharmacy. Although the data relate only to England, annual data on alcohol dependence prescriptions from Scotland suggests similarly low levels of nalmefene uptake (The Scottish Public Health Observatory, 2019).

The use of a time series analysis has offered an opportunity to examine the impact of nalmefene in a real-world setting, and one in which randomisation is inappropriate or not possible (Kontopantelis et al., 2015a). However, some assumptions and limitations relate to the analysis. Firstly, the model assumed that the 'intervention' (the NICE TA) would have an immediate impact on prescribing rather than a lagged effect, in line with prior evidence (Wathen and Dean, 2004; Curtis et al., 2018). Secondly, the model assumed that the trends are linear and not affected by anything other than the intervention under investigation (Kontopantelis et al., 2015a). In reality, a range of other factors (some of these discussed in Chapters 6 and 7) may have influenced nalmefene prescribing, although it was not possible to control for these in the model. Despite these limitations, the model fit (as demonstrated by the high *R*-squared statistic) was good (see Appendix 2, Table 6). Finally, although the mixed Poisson model suggests that fewer items per month are prescribed on average by 'standard' GP practices in comparison with 'non-standard' practices (specialist providers), this should be interpreted with caution, as the data do not fully represent prescribing done outside of 'standard' GP practices.

No statistical tests for seasonality were conducted, as these tests have been shown to be problematic when used with data consisting of a relatively small number of timepoints (Pickup, 2015). Prescribing for alcohol dependence may be subject to seasonal variations, given that alcohol consumption in some countries peaks at certain times of the year (Lemmens and Knibbe, 1993; Uitenbroek, 1996; Silm and Ahas, 2005) and that attempts to reduce drinking may be higher in January (De Vocht et al., 2016).

CPRD data

The CPRD database is highly validated and quality assured and has been used widely in epidemiological research (Herrett et al., 2010, 2015). Although the database is derived from a sample of GP practices in the UK (around 8%), it is large and patients are broadly representative of the UK general population in terms of age, sex and ethnicity (Herrett et al., 2015).

Because only a small number of patients (*n*=261) in the database had received nalmefene during the study period, it was possible to obtain data for all of them for this study. However, the small number of patients placed limitations on the types of analyses conducted. No geographical area analysis was possible due to the potential risk of identifying indidivual patients. Patient-level deprivation status was not obtained, as this was only available for a subset of CPRD patients, and would have further reduced the number of patients who had been prescribed nalmefene available for analysis. It was not possible to examine sub-groups of patients (including those who taking nalmefene for longer periods or who have received more prescriptions) due to the small number of patients.

Other limitations relate to the nature of routinely collected health data from primary care (Herrett et al., 2015). Data recording can vary among GPs, resulting in incomplete, inconsistent or missing data (O'Donnell, 2014; Khadjesari et al., 2017; Thompson et al., 2017) or misclassification of some diseases (Herrett et al., 2015). High levels of missing data on alcohol are linked with poor identification of alcohol problems in primary care; a reluctance to record diagnoses that are potentially stigmatising; a failure to regularly update alcohol information; and using the freetext area of the patient record database to record alcohol information (which is not available to researchers) (Cheeta et al., 2008; Khadjesari et al., 2013; Stewart et al., 2017; O'Donnell et al., 2018; Mansfield et al., 2019). Other issues relate to the accuracy of alcohol data, including that it is based on self-reported information from patients, in which there is under-reporting (Khadjesari et al., 2013) and that GPs are inconsistent in how they record alcohol diagnoses (Cheeta et al., 2008).

These issues have introduced uncertainty into some of the findings. The relatively out-of-date drinking data for many patients who had been prescribed nalmefene, and the fact that a fifth of them had no weekly unit consumption data in their records, means it is difficult to be sure about the proportion of patients meeting the 'high DRL' requirement for nalmefene. The proportion with an alcohol dependence diagnosis may be higher, assuming that this is under-

recorded by GPs. Read codes used to identify alcohol dependence may not have captured those with mild alcohol dependence (Thompson et al., 2017). Psychosocial support relating to nalmefene treatment may not have been recorded in the GP record for some patients or may have been recorded elsewhere, especially if it has been delivered by specialist services.

Assessments of prior alcohol treatment and the extent to which patients are newly presenting to their GP for alcohol problems are also subject to some uncertainty given that some of this data may not be fully recorded. Consequently, more nalmefene patients may have received prior alcohol treatment than the 50% reported in this study, and the 17% who are newly presenting for their alcohol problems may be an over-estimate (assuming that alcohol problems are under-recorded).

The assessment of alcohol-related comorbidity centres on a small number of conditions (depression, anxiety, gastrointestinal disorders and alcohol-related liver problems) for which it was relatively straightforward to identify associated medications or Read codes. However, a wide range of different codes could have been used to identify a disease or condition (Springate et al., 2014). Whilst the prescription data in primary care records is robust (Herrett et al., 2010; Francis et al., 2017), these are not directly linked to specific diagnoses or conditions (Francis et al., 2017). The variable for receipt of another alcohol dependence medication included two drugs whose main indication is not for alcohol dependence (baclofen is indicated for skeletal muscle disorders whilst topiramate is for epilepsy and seizures). An assumption was made that the small proportion of patients who had been prescribed nalmefene who had previously been prescribed these drugs (3%) had received them for their alcohol problems (although this was not verified in the data).

Finally, information about the nalmefene prescriptions received by patients is based on a snapshot of their data from May 2013 to June 2017, and no information about subsequent prescriptions after this date was obtained. Some patients may therefore have continued to receive prescriptions beyond June 2017, which will have an impact on some of the findings, for example, duration of prescribing. Determining how individual patients actually use the drug is challenging, as there is no certainty that they are actually taking the drug; the 'as-needed' nature of nalmefene adds to this challenge.

CPRD data are complex, requiring considerable data management time and an understanding of how GP data are structured and recorded in clinical practice (Herrett et al., 2015). To assist

this process, pre-defined and validated codelists have been used where possible to improve the validity of the analyses, including those listed at the Clinical Codes Repository (Springate et al., 2014). Advice from clinicians was also sought in relation to constructing some of the analysis variables, and details of how these have been constructed have been included. All codelists used in the analysis have been made available in the appendix to this chapter (Appendix 2).

5.6 Summary and conclusion

Levels of nalmefene prescribing in UK primary care were low, even more so than for other drugs used for alcohol problems. The publication of the NICE TA was a key influence on prescribing levels, which increased significantly at that time. Patients who were prescribed nalmefene in primary care practice in the UK were more likely to be female and to have comorbid conditions than those who participated in the clinical trials. The findings suggest that many patients may not have received the drug in line with the licensing conditions, in that they did not have an alcohol dependence diagnosis, were not drinking at a high DRL, had not received a pre-nalmefene assessment and did not receive adjunct psychosocial support. Although this suggests that GPs may have difficulties in meeting these very specific criteria, these findings should be interpreted with caution due to limitations in the GP data including possible under-recording of alcohol data and the fact that patients may have received psychosocial support outside of primary care that was not captured by the GP data. Whilst nalmefene may have enabled GPs to engage some new patients into alcohol treatment for the first time, this is subject to some uncertainty, given the high levels of GP contact and comorbidity among patients combined with known issues relating to under-recording of alcohol data. It is also notable that most patients who had been prescribed nalmefene received only one prescription of the drug. This finding, alongside other reported prescribing patterns and possible influences on these, are discussed further in Chapter 7.

6 STUDY 2: PHARMACEUTICAL MARKETING AND ITS POTENTIAL INFLUENCE ON UPTAKE OF NALMEFENE: A DOCUMENTARY ANALYSIS

6.1 Introduction

This thesis describes patterns in, and influences on, nalmefene prescribing in UK primary care. The weaknesses in the evidence on nalmefene efficacy (Chapter 3) raised questions about its place as a treatment recommended by national guidance. This chapter focuses on pharmaceutical marketing activities (Chapter 2), which may also influence prescribing. The chapter draws on publically available documents to describe the marketing activities undertaken for nalmefene and, as far as possible, to understand their potential role in how it was subsequently adopted in practice.

The World Health Organisation (WHO) define pharmaceutical promotion as "*all informational and persuasive activities by manufacturers and distributers, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs*" (WHO, 1988, p. 2). New forms of pharmaceutical promotional activity include engagement with networks of 'stakeholders' who may have some influence in the prescribing environment (Edgar, 2013). Stakeholders may include governments, formulary committees, regulatory bodies, pharmacists, hospital managers, patients and patient organisations (Pesse et al., 2006; Hastings and de Andrade, 2016). Stakeholder marketing allows organisations to develop potentially beneficial relationships with other organisation or individuals (Hastings and de Andrade, 2016).

6.2 Aims and Objectives

The aim of this study was to identify and review publically available documentation to describe the marketing of nalmefene and examine its potential role in the way in which the drug was perceived and used in the UK. In this chapter, the term 'marketing' is used to refer to interactions and activities undertaken by Lundbeck at the time when the company was seeking to promote nalmefene in the UK. The specific objectives were to:

- describe how nalmefene has been promoted through the academic literature including the role of Lundbeck in the relevant papers;

- identify and examine key messages about nalmefene or alcohol treatment more widely in academic publications;
- identify and describe other alcohol-related activities undertaken by Lundbeck to promote nalmefene in the alcohol field;
- identify and examine key messages about nalmefene (or alcohol treatment more widely) in these other activities;
- identify and describe the organisations involved in the range of marketing activities for nalmefene and how they are connected; and
- examine the transparency of Lundbeck involvement in these activities.

6.3 Method

6.3.1 Introduction to documentary analysis

Documentary analysis is an established qualitative research method (Bowen, 2009), described as "*a mechanism and vehicle for understanding and making sense of social and organizational practices*" (Coffey, 2013, p. 2). It can provide context, identify new research questions, provide additional data, monitor change or verify findings (Bowen, 2009). Documents included can vary widely in format and type, including agendas, minutes from meetings, event programs, letters, news articles, press releases, organisational reports and many more (Bowen, 2009).

The approach used to analyse documents can also vary (Prior, 2003; Silverman, 2006), although most analyses involve some combination of document retrieval, content review and data synthesis (Bowen, 2009). Both the content of documents and the social context in which documents are produced (including their authorship and readership) enable understanding of social and organisational practices (Coffey, 2013). It is important to understand who has produced documents as "*every document is packed tight with assumptions and concepts and ideas that reflect on the agents who produced the document*" (Prior, 2011, p. 18). Furthermore, the information they relay can be framed in particular ways in order to influence the reader's interpretation (Entman, 1993; Carter, 2013).

6.3.2 Approach and rationale

Drug companies' marketing activities can be multifaceted, and documentary analysis is an ideal and practical method of capturing this diversity as documents are readily available, capture most events, and can often be accessed online (Bowen, 2009). Documents also benefit from their 'exactness' and 'coverage' (Yin, 1994), with detailed data on events and other phenomena which may not easily be obtained elsewhere and which do not rely on participant recall. These features make this an effective method of gathering information about nalmefene marketing.

This analysis draws on Prior (2003), who describes three important aspects of analysing documents – production, use, and content. Documents are produced in 'socially organised circumstances' and have 'effects', and it is therefore sensible to ask questions about their production and use (Prior, 2003). This analytical approach is relevant here because drug marketing can involve a wide variety of stakeholders with potential influence over prescribing. This analysis therefore considers not only the content of documents, but also how they have been produced, authored, and used in ways that may help facilitate nalmefene uptake.

6.3.3 Identifying the documentary materials

Two sources were used: (i) published academic literature; and (ii) grey literature which were identified as outlined below.

6.3.3.1 Academic literature

Peer-reviewed academic journal papers were examined. Papers were identified using the systematic search previously outlined in Chapter 3, Section 3.2, but covering the period only from 2010 to 2017. Papers were included if they reported Lundbeck-sponsored RCTs or secondary analysis of these; were systematic reviews or meta-analyses including nalmefene; were narrative reviews including nalmefene; were other clinical studies of nalmefene for reducing alcohol consumption; or were other studies related to alcohol treatment. Conference abstracts, commentaries, editorials and letters were excluded.

6.3.3.2 Grey literature

The term 'grey literature' is used throughout this thesis to refer to documents that have not been published in the same way as academic papers, for example, government papers or

organisational reports (Haddaway et al., 2015). A snowball approach was used to obtain such documents relevant to how nalmefene was promoted, with a focus on alcohol-related activities that were funded or supported by Lundbeck. Firstly, I used information and documents gathered from six key informants (individuals who have researched nalmefene as well as some sampled for the qualitative study) and preliminary online searches, to identify organisations and individuals involved in nalmefene work. I used this information to design and conduct more refined Google searches. Online results pages were scanned until results were no longer relevant (scanning was stopped after 5 pages of irrelevant results), and relevant documents obtained. Activities were excluded if they were unrelated to alcohol or conducted outside of the UK. Identified media reports were not analysed directly but skimmed for relevant links. Advanced Google searches were conducted between October 2018 and March 2019 (Box 1).

Box 1: Grey literature search strategy

- Lundbeck AND (Nalmefene OR Selincro)
- Lundbeck AND Alcohol
- Lundbeck AND (names of organisations identified from preliminary searches, documents provided by key informants, or conversations)
- Lundbeck AND (names of individuals identified from preliminary searches, documents provided by key informants, or conversations)
- (Nalmefene OR Selincro) AND (names of organisations identified from preliminary searches, documents provided by key informants, or conversations)
- (Nalmefene OR Selincro) AND (names of individuals identified from preliminary searches, documents provided by key informants, or conversations)
- Searches of organisational websites were conducted in December 2018: Lundbeck (https://www.lundbeck.com/global), National Institute for Health and Care Excellence (https://www.nice.org.uk/), Scottish Medicines Consortium (https://www.scottishmedicines.org.uk/), Alcohol Concern (https://alcoholchange.org.uk/), British Liver Trust (https://britishlivertrust.org.uk/). Searches of some organisational websites were conducted using the Wayback Machine (an Internet archiving web site), to check for archived reports no longer present on the current website (*The Wayback Machine*, no date).

6.3.4 Analysis of the academic literature

The full text of the academic papers including supplementary files was obtained where possible. Relevant data from each paper were summarised under key headings and coded as in Table 20. Headings were informed by initial reading of selected papers and prior knowledge of other literature discussed in Chapters 2 and 3. These were further refined in discussion with my lead academic supervisor and entered onto an Excel spreadsheet.

Table 20: Coding framework for academic literature

Headings	**Extracted information**	**Coding**
Title & author	Title as on paper	
Publication date	Date on paper	
Paper type	Extracted from methods sections	OT: original trial of nalmefene efficacy SA: Secondary analysis of nalmefene RCT data SR/MA: Systematic review and/or meta-analysis of nalmefene (efficacy) Other SR/MA: systematic review and/or meta-analysis of nalmefene (non-efficacy) Other N: other study of nalmefene (not clinical trials) NR: Narrative reviews including nalmefene OS: Other studies relating to alcohol treatment
Main focus of paper	Qualitative description	1. Nalmefene efficacy 2. Nalmefene safety 3. Wider benefits of nalmefene (health/public health/costs) 4. Clinical relevance of nalmefene/reducing consumption 5. As-needed regimen approach 6. Pharmacological approaches for alcohol problems 7. Reduced-drinking approaches 8. Alcohol treatment/approaches to treatment 9. Treating liver disease 10. Primary care management of alcohol problems 11. Prevalence of AUDs
Overall conclusion on nalmefene (based on current evidence)	Qualitative description, with verbatim extracts	1. Efficacious 2. Not efficacious 3. Not proven 4. Nalmefene not discussed 5. Unclear – abstract only
Inclusion of critical commentary on nalmefene: Includes general concerns about the value of nalmefene or discussion of limitations relating to its evidence: the small effect size for nalmefene compared with psychosocial support alone; lack of comparison with any other drug; the post-hoc sub-group analysis; the high level of missing data; side effects concerns; challenges in meeting the licensing conditions; or lack of generalisability.	Qualitative description, with verbatim extracts	1. Yes some 2. None at all 3. Unclear – abstract only

Inclusion of concepts/ideas/themes supporting the use of nalmefene	Qualitative description, with verbatim extracts	1. New/novel 2. Engaging new patients 3. Unmet need 4. As-needed use 5. Patient-centred 6. Clinical relevance of nalmefene 7. Cost-effectiveness of nalmefene 8. Health/public health benefits of nalmefene 9. Promotes reduced drinking approaches 10. Greater role for primary care 11.Greater use of pharmacological approaches 12. Unclear – abstract only
Overall level of support for nalmefene	Based on overall conclusion, level of critical commentary, and inclusion of concepts/ideas supporting nalmefene	1. Supportive overall (no critical discussion) 2. Supportive overall (some critical discussion) 3. Unsupportive (cannot recommend based on current evidence) 4. Neutral (no comments on benefits/otherwise) 5. Indirectly supportive (non-nalmefene papers funded by Lundbeck but discussed concepts/ideas supporting its use)[1] 6. Unclear – abstract only
Papers classed as 'COI' include those where there is/are: (a) A financial payment from Lundbeck to authors (speakers fees, honoraria, consultancy, research or educational funding, travel, accommodation) (b) Authors who are Lundbeck employees or individuals from organisations appointed by Lundbeck (c) Authors who were part of the Lundbeck Advisory Board for nalmefene. (d) Authors with a COI declared elsewhere		1. COIs declared 2. Declared that no COIs 3. Paper has no information about COIs 4. Unclear – abstract only 5. Complex
Disclosure of Lundbeck funding: Any declaration of funding for the work (either the study itself was funded or funding was provided for the preparation of the paper (i.e. writing or editorial assistance).		1.Yes 2. No 3. Unclear – abstract only 4. Complex 5. Paper has no information about COIs/funding

1. Supportive themes: support for more alcohol treatment, support for pharmacological approaches, support for reduced drinking and primary care interventions.

A second researcher from the University of Stirling (Kathryn Angus) reviewed the extraction of data from a 10% sample of the academic papers using the same protocol. Some small

additional details were identified by Reviewer 2 (and applied to all papers). For one paper, Reviewers 1 and 2 differed in their rating of overall support for nalmefene, and this was later agreed through discussion.

Given the importance and influence of meta-analytic systematic reviews, all meta-analyses of nalmefene efficacy were assessed for bias using the ROBIS risk of bias tool (Whiting et al., 2016). The results of this element are discussed in Section 6.4.1 below.

6.3.5 Analysis of the grey literature

An initial review of the identified documents was used to develop a Microsoft Excel-based coding framework into which each document was coded, as outlined in Table 21. A second reviewer (Kathryn Angus) blind-reviewed a 20% sample of the documents (selected to cover all four activities and a range of document types using the same protocol. Coding results were compared, minor discrepancies discussed, and overall results were re-checked for consistency, resulting in some activities receiving additional 'key message' codes and the transparency level being revised for a few activities.

Table 21: Coding framework for grey literature

Heading	Extracted information	Coding
Document name	Title as on document	
Date	Date of publication or event date	
Document type	See coding list	1.Conference flier 2. Meetings (agendas/minutes) 3. Local guidelines 4. Online planning tool 5. Presentation slides 6. Web page 7. Policy submission 8. Joint working agreement 9. Online news article 10. Report 11.National advisory body guidance
Activity identified	See coding list	1. Report 2. Event 3. Planning tool 4. Policy submission
Whether nalmefene mentioned	Yes/No	1. Yes 2. No
Key messages about nalmefene	Qualitative description, with verbatim extracts	1. Introducing/raising awareness of nalmefene 2. How to prescribe nalmefene 3. Efficacy 4. Novelty

		5. Reduced drinking 6. Unmet need 7. Engaging patients into treatment 8. Guidance on implementing nalmefene 9. Local care pathways
Focus, purpose, key messages of the activity	Qualitative description, with verbatim extracts	1. Awareness of alcohol harms 2. Reducing alcohol harms 3. Investment in alcohol treatment 4. Identifying problem drinkers 5. Needs of hazardous/harmful drinkers 6. Reduced drinking 7. Pharmacotherapy 8. Primary care role 9. Screening 10. Patient care pathways/ICPs 11. Following NICE guidelines 12. Implementing nalmefene 13. Alcohol issues/treatment/services 14. Online psychosocial support 15. Alcohol dependence 16.Treatment goals 17. Alcohol and adolescence 18. Addressing comorbidities
Nature of Lundbeck funding	Qualitative description, with verbatim extracts	1. Report: no Lundbeck editorial control 2. Report: 'partnership'(Lundbeck editorial/ writing assistance provided) 3. Report: written by/for Lundbeck 4. Report: unclear if Lundbeck had any role in editing/writing 5. Event: Secretariat costs 6. Event: Lundbeck organised/sponsored meeting 7. Event: Lundbeck-sponsored conference workshop/session 8. Event: Lundbeck-sponsored network meetings 9. Event: Lundbeck funded conference costs 10. Planning tool: joint/partnership working with Lundbeck 11. Planning tool: Lundbeck funded 12. Lundbeck submission
Transparency of Lundbeck involvement	Qualitative description, with verbatim extracts	1. Funding disclosed with details on Lundbeck role or how funding was used ('Detailed') 2. Funding disclosed but unclear on aspects of Lundbeck role or how funding was used ('Some') 3. Funding disclosed but no details on Lundbeck role or how funding was used ('Lacking')
Key organisations involved	Named	

Once coding was complete, the number of activities of each type was counted, and the remaining extracted details summarised, including (where appropriate) the presence of any narratives directly or indirectly supportive of nalmefene. Documents were reviewed to identify organisations, stakeholders and stakeholder types, and activities in which they were engaged. This list was used to create a diagram illustrating how various stakeholder types were connected with the promotional work for nalmefene (Section 6.4.3).

6.4 Results

6.4.1 Academic literature

Ninety published papers met the inclusion criteria (Section 6.3.3.1) and are outlined in full in Appendix 3, Table 1. Of the ninety papers, 59% (*n*=53) included at least one author with a potential Lundbeck COI, as defined in Table 20 above, including at least two papers where author COIs were not disclosed. Lundbeck funding was declared in 24 of the 53 papers, plus one additional paper in which no COIs were declared. Funding was reported as for the research and/or for preparing the paper. Funded papers amounted to 28% of all papers identified (Table 22).

Table 22: Scientific papers identified in the literature search

Type of paper	COIs declared in papers[1]			Funding declared			Total
	LB COIs	No LB COIs	Insufficient information [2]	LB funding	No LB funding	Insufficient information [2]	
Nalmefene RCTs	3	-	-	3	-	-	3
Secondary analysis of RCT data	11	-	-	11	-	-	11
Systematic reviews or meta analyses including nalmefene	10[3]	3	-	3	10	-	13
Other studies of nalmefene (not clinical trials)	1	2	-	1	2	-	3
Narrative reviews including nalmefene	21	16	16	2	36	15	53
Other studies relating to alcohol treatment	7	-	-	5	2	-	7
All	**53**	**21**	**16**	**25**	**50**	**15**	**90**

1. See definition of COI given in Table 20. Two papers did not declare any Lundbeck COIs but their authors had declared these in other published papers.
2. COI status for 16 narrative reviews was uncertain: 8 had no COI section; 6 were abstract only; and in 2 the COI status was complex. These 2 were written by an author affiliated to a medical publisher, and who has also reviewed other Lundbeck products. The 'Disclosure' section in both papers states that during the peer review process Lundbeck was offered an opportunity to comment on the drafts; among the list of manuscript reviewers are nalmefene trial authors.
3. Three papers critical of nalmefene are listed as having LB COIs due to an author (the same author) declaring receipt of Lundbeck funding to cover travel, accommodation and expenses relating to a conference presentation; this author declared that other fees were offered but not accepted.

6.4.1.1 Nalmefene RCT papers

The results of the Lundbeck-sponsored nalmefene RCTs were first reported in three clinical trials papers, which report funding by the drug company (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014a). All the papers are supportive of the use of nalmefene. Although they discuss general limitations of RCT evidence, including attrition and exclusion of patients with comorbidities, there is little discussion of other trial limitations. For example, in all the trials, nalmefene was delivered alongside an extensive programme of psychosocial support delivered to both the treatment and placebo patients, but the papers include little commentary

on this, stating only that there were substantial reductions in alcohol consumption in the placebo group.[21] Superiority of nalmefene over the placebo is claimed in the papers, which also claim that small differences in reductions in alcohol consumption reported in patients given nalmefene compared to those given placebo treatment are "*relevant*" in clinical terms (Mann et al., 2013; van den Brink et al., 2014a). None of the papers mention psychosocial support in their abstracts, and only brief coverage of this is included in the main text.

Prominent themes across these trial papers include claims that nalmefene is 'new' or 'novel' due to its focus on reduced drinking and its 'as-needed' regimen and the suggestion that it therefore had the potential to engage new patients into treatment:

> *The nalmefene treatment paradigm thus addresses an unmet medical need as it obviously has the potential to engage alcohol dependent patients in treatment who may otherwise not have sought help.* (Gual et al., 2013, p. 1439)

> *... constitutes a potential new pharmacological treatment paradigm in terms of the treatment goal and dosing regimen, and provides a method to address the unmet medical need in patients with alcohol dependence that need to reduce their alcohol consumption.* (Mann et al., 2013, p. 706)

Support for a reduced-drinking approach is also evident in the original trial papers:

> *Reduction of alcohol consumption is associated with reduced risk of morbidity and mortality in patients with alcohol dependence.* (Mann et al., 2013, p. 706)

> *… reduced drinking is increasingly accepted as a viable treatment goal by professionals and official agencies.* (van den Brink et al., 2014a, p. 733)

[21] For example, from ESENSE 2: "Compared with baseline, there was a substantial reduction in alcohol consumption in both treatment conditions on both co-primary outcome measures: number of heavy drinking days and total alcohol consumption decreased by approximately 65% in the nalmefene group and by approximately 60% in the placebo group" (Gual et al., 2013). Similar wording is used in ESENSE 1 (Mann et al., 2013).

6.4.1.2 Papers based on secondary analysis of nalmefene RCTs

Also produced with Lundbeck funding were eleven papers reporting secondary analysis of the three nalmefene RCTs, all but one using findings from patients included in the post-hoc sub-group analyses (see Section 3.3.3). All support nalmefene in reducing alcohol consumption, and many fail to critically discuss the limitations of the RCT evidence. Some papers focused on the clinical relevance of nalmefene or a harm reduction or reduced-drinking approach more generally (François et al., 2014; Aubin et al., 2015; Roerecke et al., 2015) or cost effectiveness of nalmefene treatment (Laramée et al., 2014; Brodtkorb et al., 2016; Laramée et al., 2016b). Other purported benefits of nalmefene included quality of life (François et al., 2015), public health (Laramée et al., 2016b), patient adherence (Sinclair et al., 2014), and safety/tolerability (van den Brink et al., 2015). For example:

> *Nalmefene demonstrates considerable public benefits by reducing alcohol-attributable productivity losses and crime events in adults with both alcohol dependence and high or very high DRLs who do not require immediate detoxification and who have high or very high DRLs after initial assessment.* (Brodtkorb et al., 2016, p. 163)

> *... demonstrate considerable public health benefits of reducing alcohol-attributable harmful events through the use of nalmefene with psychosocial support.* (Laramée et al., 2014, p. 16)

6.4.1.3 Systematic reviews or meta-analyses including nalmefene

Thirteen systematic reviews or meta-analysis papers were identified, ten of which concern the efficacy of nalmefene, and are discussed here (Table 23).

Table 23: Systematic review papers on nalmefene efficacy (*n*=10)

Type	Lundbeck involvement	Independent
Systematic reviews (*n*=4)	Barrio and Gual, 2016 Soyka et al., 2017	Fitzgerald et al., 2016 Naudet et al., 2016a[2]
Systematic reviews with meta-analyses (*n*=6)	Rösner et al., 2010a[1] Mann et al., 2016 (Lundbeck-funded) Soyka et al., 2016 (Lunbeck-funded)	Jonas et al., 2014 Palpacuer et al., 2015[2] Palpacuer et al., 2017[2]

1.This review, conducted prior to publication of results from the Lundbeck RCTs, did not make a final conclusion on nalmefene due to insufficient patient numbers.
2. COI was related to one author's receipt of travel/accommodation expenses from Lundbeck for speaking at a conference (for which he refused speaker fees).

The efficacy systematic reviews arrived at contrasting conclusions about nalmefene. Five conclude there is insufficient evidence for the drug (Rösner et al., 2010b; Palpacuer et al., 2015, 2017; Fitzgerald et al., 2016; Naudet et al., 2016a); one of these (Rösner et al., 2010b) was conducted prior to the Lundbeck RCTs). The other five conclude that it is efficacious (Jonas et al., 2014; Barrio and Gual, 2016; Mann et al., 2016; Soyka et al., 2016, 2017). Among the meta-analyses there are also divergent results. Those with relatively stronger links to Lundbeck conclude in favour of nalmefene (Mann et al., 2016; Soyka et al., 2016), whilst other more independent reviews conclude there is either moderate evidence for some outcomes (Jonas et al., 2014) or insufficient evidence to support nalmefene prescribing (Palpacuer et al., 2015, 2017). An assessment of risk of bias in these meta-analyses using the ROBIS risk of bias in systematic reviews tool (Whiting et al., 2016) suggests a high risk of bias in the industry-supported meta-analyses of nalmefene (Table 24).

Table 24: ROBIS Assessment of risk of bias in the nalmefene systematic reviews with meta-analyses

	Phase 2				Phase 3
Review (first author and year)[1]	**Study Eligibility Criteria**	**Identification and Selection of Studies**	**Data Collection and Study Appraisal**	**Synthesis and Findings**	**Risk of bias in the review**
Jonas 2014	Low	Low	Low	Low	Low
Palpacuer 2015	Low	Low	Low	Low	Low
Mann 2016	Low/Unclear	Low/Unclear	High	High	High
Soyka 2016	High	Low	High	High	High
Palpacuer 2017	Low	Low	Low	Low	Low

1.The Rosner meta-analysis was not assessed as it occurred prior to the Lundbeck RCTs.

6.4.1.4 Other clinical studies of nalmefene

Three papers reported small-scale non-randomised and/or uncontrolled studies of nalmefene, reporting reductions in alcohol consumption among nalmefene patients (Appendix 3, Table 1). Of these, one declared COIs relating to Lundbeck (Owens et al., 2015), and another (Di Nicola et al., 2017), Lundbeck funding. The latter evaluated nalmefene in patients with AUD and stabilised psychiatric comorbidity and concluded that it "*is a valid therapeutic option in real-world clinical settings, where comorbid conditions are common*" (p. 1636). The authors also claim that nalmefene could engage patients who may otherwise not have sought help for their alcohol problems. All three refer uncritically to the nalmefene trials.

6.4.1.5 Narrative reviews of nalmefene

There were 53 narrative reviews, focusing on pharmacological management of alcohol problems (*n*=28); nalmefene specifically (*n*=9); approaches to alcohol treatment (*n*=8); reduced-drinking approaches (*n*=6); and liver disease (*n*=2) (Appendix 3, Table 1). In 16 reviews the COI status was unknown (8 had no COI section, 6 were abstract only, and in 2 it was difficult to discern the COI status, as noted under Table 3, note 2). 21 of the other 37 (57%) had a potential COI due to Lundbeck involvement. Of the total of 53, most reviews (*n*=37) were supportive of nalmefene to varying degrees, including almost all papers with (19/21) and some without (9/16) detectable COIs or where COIs were unknown (also 9/16). Considering only supportive reviews, 32 out of 37 (86%) failed to include any critical

analysis of the evidence base for nalmefene, tending to refer briefly to the trials as showing efficacy:

> *... pharmacological treatments: acamprosate, naltrexone and nalmefene, all of which have good evidence from modern trials of efficacy.* (Nutt and Rehm, 2014, p. 6)

These supportive narrative reviews reiterated themes from the Lundbeck trial papers on novelty, potential to engage a wider group of patients in treatment, and the idea of nalmefene as a 'patient-centred' approach:

> *... a paradigm shift in the treatment of low-severity alcoholism.* (Guardia-Serecigni, 2015, p. 5)

> *... potential to engage more patients in treatment.* (Keating, 2014, p. 10)

> *This is a patient-centred approach that engages patients with alcohol dependence in the active management of their illness.* (Luquiens and Aubin, 2014, p. 1350)

Four narrative reviews (all without any COIs relating to Lundbeck) were unsupportive of nalmefene, being critical of the trial evidence (Yancey and Lumbad, 2011; Prescrire, 2014; Goh and Morgan, 2017) and its uncertain role in treatment (Wackernah et al., 2014).

6.4.1.6 Other studies relating to alcohol treatment

Seven papers related to alcohol treatment more widely, three specifically in primary care, all of which declared Lundbeck COIs (five were funded or supported by Lundbeck) (Appendix 3, Table 1). One paper, about GP attitudes to managing alcohol problems, gives prominence to pharmacotherapy (mentioned in its abstract) and also cites nalmefene as being efficacious (Anderson et al., 2014); the paper was co-authored by the leader of one of the Lundbeck nalmefene trials (a COI omitted in the original paper but added later as a correction). Common themes in these papers include support for greater primary care involvement in addressing alcohol problems, greater use of pharmacological approaches, and promotion of a harm reduction approach:

More recently, the use of medication to support reduction in alcohol consumption offers new treatment options for patients with alcohol dependence in routine primary care. (Kraus et al., 2017, p. 290)

6.4.2 Grey literature

Thirty-nine documents relating to thirty relevant activities undertaken or supported by Lundbeck were identified (Tables 25 and 26). These are reported by type, followed by a synthesis of the key stakeholder organisations involved. A more detailed description of each funded activity is provided in Appendix 3 (Table 2).

Table 25: Types of activities funded by Lundbeck

Type of activity	Number of activities identified
Reports related to alcohol treatment	13
Events	12
Alcohol service planning tools	3
Alcohol-related submissions to policy groups	2

6.4.2.1 Lundbeck-supported reports relating to alcohol treatment

Thirteen Lundbeck-supported reports were identified, focussing on aspects of alcohol treatment (Table 26, R1–R13). Two were directly about nalmefene, one of these (R4) a Lundbeck-produced 'Advance Planning' document sent to NHS managers to raise awareness of nalmefene and its benefits in advance of its UK launch. Another (R11) was authored by the NICE Implementation Collaborative (a partnership between NHS, healthcare bodies, NICE and the ABPI) and discussed implementation of the NICE recommendation on nalmefene.

Other reports were not specifically about nalmefene but focused on increasing investment in, or access to, alcohol treatment (R1, R2, R3, R7, R9, R10), increasing the primary care role in alcohol treatment (R5), treatment goals (R6), reduction approaches in alcohol treatment (R8), coverage of alcohol-related harm in local planning documents (R9), raising awareness of health conditions associated with alcohol (R12), and interventions to reduce alcohol harms (R13). Nine reports were published by or had input from national charities, and two had introductory sections from MPs or government Ministers. Two (R6, R8) were written by Lundbeck-funded expert groups, and others involved contributions from a range of stakeholders, including NHS commissioning bodies, charities and experts. Lundbeck's

reported role in these varied: no editorial input (R13), aside from accuracy checks (R11, R12); a 'partnership' approach suggesting some editorial or writing input (either editorial or writing assistance was provided by a medical communications company or a statement that Lundbeck "*partnered*" with the organisation in producing the report) (R1, R3, R8, R9); and reports written by or for (using medical writers) Lundbeck (R4, R7, R10).

The details disclosed in some of these Lundbeck-funded reports did not provide enough information to determine their level of involvement. One report stated that it was "*part-funded*" by Lundbeck without any further details (R2); two reports reported involvement of a medical communications company used by Lundbeck but their role was unclear (R1, R9). Another (R7) was described as "*an independent report initiated and sponsored by Lundbeck*" but it is unclear who was the lead author. Many of these reports also drew on the work of other Lundbeck-funded studies or reports.

There were six common themes: a focus on alcohol treatment; reduced-drinking approaches; support for drinkers without severe dependence; early screening and primary care interventions; integrated care pathways; and implementation of NICE guidelines. Firstly, the majority of the Lundbeck-supported reports argued the case for and highlighted current gaps in alcohol treatment, rather than public health or prevention policies. Some reports aligned alcohol treatment with wider public health policy approaches:

> *Commissioners should "invest to save" and increase funding for alcohol treatment services.* (British Liver Trust, 2012, p. 7)

> *Research demonstrates that treatment for alcohol dependence "not only helps the individuals affected, but also substantially improves public health in general".* (Gilbert, 2014, p. 22)

Secondly, many reports advocated for a reduced-drinking approach to addressing alcohol problems, with some mentioning its potential to engage a wider group of people into alcohol treatment:

> *... the British Liver Trust notes that offering the option of reduced drinking may lead to less severely dependent problem drinkers, who may not want to access abstinent-focussed services, being recruited into treatment*. (Gilbert, 2014, p. 14)

> *By providing an additional intervention to implement a reduction strategy, nalmefene may encourage the alcohol dependent patient to seek treatment earlier.* (Lundbeck Ltd., 2012, p. 5)

In several of the reports, the argument is made for more interventions aimed at individuals with mild alcohol dependence and those drinking at hazardous and harmful levels, or for early targeted screening and primary care management of alcohol problems. For example:

> *… specialised services … are not equipped to meet the needs of the much larger groups of 'hazardous' and 'harmful' alcohol mis-users*. (Alcohol Concern, 2011, p. 19)

> *Only by investing in targeted screening, brief interventions and treatment, particularly within the primary care setting, can we begin to achieve changes in outcomes for those who are drinking hazardously or harmfully and are mildly dependent.* (Gilbert, 2014, p. 9)

> *This study suggests that targeting people with chronic diseases, particularly hypertension and epilepsy, is an effective approach to both screening and achieving behaviour change.* (Coetzee et al., 2013, p. 13)

Fifthly, the reports raise the importance of implementing integrated care pathways (ICPs) for alcohol. ICPs outline the various stages in the care of patients affected by a specific health condition (Campbell et al., 1998) and the development of such pathways for alcohol was also funded by Lundbeck (as discussed in Section 6.4.2.3 below).

> *An integrated care pathway should be developed detailing essential steps in the care of patients with all levels of alcohol misuse.* (Gilbert, 2014, p. 6)

> *… developing robust local pathways for pharmaceutical adjuncts to psychosocial treatments.* (NICE Implementation Collaborative, 2015, p. 20)

Finally, several reports recommended adherence to NICE prescribing guidelines:

> *Commissioners should audit services to ensure that they follow NICE and other appropriate national and local guidelines …* (British Liver Trust, 2012, p. 22)

> *Commissioners should ensure that alcohol treatment services follow NICE and other appropriate guidelines.* (Lundbeck Ltd., 2012, p. 4)

6.4.2.2 Lundbeck-sponsored events

A range of events (*n*=12) were identified which had funding support from Lundbeck (Table 26, E1–E12). These included four large-scale conferences held by alcohol charities, and which were aimed at a wide audience, including clinicians, alcohol services, researchers and policy makers (E1, E3, E4, E7). The sponsored conferences included specific sessions relevant to nalmefene, one (E3) on the Lundbeck-sponsored ICP project. No information was available from the flier on whether the session was also specifically sponsored by Lundbeck or included mention of nalmefene. Another (E7) included a Lundbeck-sponsored session on "*an alternative pharmacological approach*" for reducing alcohol consumption.

Three one-off educational events, aimed at clinicians (GPs, nurses, mental health professionals) (E5, E6, E9) all included sessions on addressing alcohol problems in primary care, one specifically about online psychosocial interventions for alcohol in primary care, and another on the use of nalmefene in primary care. Other funded events included expert meetings to discuss the management of alcohol problems (E8, E10) and a network of mental health service commissioners (E12), where there were sessions on the Lundbeck-sponsored ICP project and applying NICE guidelines.

Lundbeck's funding of events and specific sessions was clearly stated in identified documents but their influence in shaping the content of these events and sessions is not known (E5, E7).

6.4.2.3 Lundbeck-funded alcohol service planning tools

Lundbeck funded the development of alcohol service planning tools (Table 26, P1–P3) to support local commissioners, working jointly with a charity (P1) and with a range of others (a charity, local commissioners, an academic network, and an expert group)(P3a to e). The Alcohol Harm Map (P1) and the Alcohol Impact Model (P2) were online resources which aimed to provide information on alcohol harms and associated costs at area level. The others related to ICPs for alcohol services (P3a to c), an evaluation of a treatment pathway for patients with increasing or higher risk drinking (P3d) and the development of an online tool for ICPs (P3e). The ICPs aimed to define a local healthcare pathway for all individuals at risk of alcohol-related harm. One detailed document was identified (Kent County Council, 2014b)

which specified one of the Lundbeck-supported ICPs (P3a) and it contains numerous references to nalmefene or to Lundbeck-sponsored products (a screening scratchcard, online psychosocial support, the Alcohol Impact Model (P2) and a report on alcohol treatment (R7)).

Lundbeck's funding is disclosed on this set of documents (P1–P3) but the exact details of their involvement or influence cannot be determined.

6.4.2.4 Lundbeck submissions to national policy consultations

Lundbeck made two submissions to national alcohol policy consultations in the UK's devolved nations, one in Wales and one in Northern Ireland (Table 26, S1–2). In these, Lundbeck advocate for additional funding for alcohol treatment, an increase in primary care interventions with individuals with milder alcohol dependence, and a harm reduction approach to alcohol treatment. One submission (S2) cited another Lundbeck-funded report (R3):

> *A radical redesign of alcohol treatment services is needed to ensure provision of services for patients at all levels of severity of alcohol dependence. Provision of identification/screening, brief interventions and treatment for those who are drinking hazardously or harmfully and are mildly dependent, particularly within the primary care setting is necessary*. (Lundbeck Ltd., 2014e, p. 4)

> *We also support the harm reduction component of community addiction services and wish to draw your attention to the evidence in the British Liver Trust's report, Reducing Alcohol Harm: recovery and informed choice for those with alcohol related health problems.* (Public Health Agency and Health and Social Care Board, 2013, p. 11)(R3)

The Wales submission references nalmefene's licensing conditions and the endorsements of nalmefene made by the Scottish and Welsh regulatory bodies, whilst the Northern Ireland submission advocates for partnership work to develop ICPs, and for pharmacological treatments specifically:

> *We look forward to the opportunity to work in partnership with the HSC and the third sector to support the development of the Integrated Care Pathway*

work, particularly in relation to alcohol harm reduction services. (Public Health Agency and Health and Social Care Board, 2013, p. 3)

We would also suggest that information on the role of pharmacological treatments alongside psychological interventions in the relevant steps of the core care pathway is included and/or signposted. (Public Health Agency and Health and Social Care Board, 2013, p. 8)

Table 26: Coding of grey literature

ID	Name	Date	Type[1]	Activity[1]	Nalmefene Y/N	Key messages on nalmefene[1]	Key messages about alcohol problems/ treatment	Nature of funding[1]	Trans-parency[1]	Organisations involved
R1	Making alcohol a health priority: Opportunities to reduce alcohol harms and rising costs (Alcohol Concern, 2011)	Jan 2011	10	1	No	NA	1,2,3,4,5,13	2	Some	Alcohol Concern Lundbeck
R2	Everyone's problem: The role of local alcohol services in tackling Wales' unhealthy relationship with alcohol (Alcohol Concern Cymru, 2012)	Feb 2012	10	1	No	NA	1,3,13,15	4	Lacking	Alcohol Concern Cymru, Lundbeck
R3	Reducing Alcohol Harm: recovery and informed choice for those with alcohol related health problems (British Liver Trust, 2012)	Feb 2012	10	1	No	NA	1,2,3,6, 11	2	Some	British Liver Trust Lundbeck Munro & Forster
R4	Nalmefene for managing alcohol dependence in primary and secondary care (Lundbeck Ltd., 2012)	May 2012	10	1	Yes	1,3,5,6	3,6,8,11,15	3	Detailed	Lundbeck
R5	Increasing primary care engagement with the alcohol harm reduction agenda: Report on a research project into the use of alcohol Identification and Brief Advice with chronic disease groups (Coetzee et al., 2013)	June 2013	10	1	No	NA	2,3,4,6,7,8,9 ,15,18	4	Some	Alcohol Concern, Lundbeck, NHS Wandsworth, alcohol experts
R6	Patient stratification: Identifying treatment goals for people with alcohol dependence (Medical Expert Steering Group on the Management of Alcohol Dependence with Lundbeck UK Ltd., 2013)	Aug 2013	10	1	No	NA	6,15,16	4	Some	Medical Expert Steering Group on the Management of Alcohol Dependence, Lundbeck
R7	15:15 The case for better access to treatment for alcohol dependence in England (Lundbeck Ltd., 2013a)	Sept 2013	10	1	No	NA	3,6,9,10, 11	3	Some	British Liver Trust, Alcohol Concern, Lundbeck
R8	Reduction of alcohol consumption as a treatment approach for alcohol dependence: What commissioners need to know (Grimm et al., 2013)	Oct 2013	10	1	No	NA	6,7	2	Detailed	ICP for the Prevention and Management of Alcohol Use Disorders in Adults Expert Advisory Group, Lundbeck
R9	An Audit of the focus on Alcohol-Related Harm in Joint Strategic Needs Assessments, Joint	Mar 2014	10	1	No	NA	1,2,10,13	2	Some	Alcohol Concern, Lundbeck Munro & Forster

	Health And Well-Being Strategies And CCG commissioning Plans (Alcohol Concern, 2014b)									
R10	Every contact counts: Improving access to treatment for alcohol misuse in Northern Ireland (Gilbert, 2014)	Aug 2014	10	1	No	NA	1,2,3,4,5,6,8, 9,10,11,13, 15,16	3	Detailed	Addiction NI, FASA, Lundbeck Chambre Public Affairs LLP
R11	Supporting local implementation of NICE Technology Appraisal 325 on reducing alcohol consumption in adults with alcohol dependence - a NIC-designated project (NICE Implementation Collaborative, 2015)	July 2015	10	1	Yes	2,8,9	4, 10,11,12	1	Detailed	NICE Implementation Collaborative (contributions from individuals with Lundbeck COIs), Oxford Academic Health Sciences Network (AHSN), Innovation Agency North West Coast AHSN, Lundbeck.
R12	Alcohol Concern factsheets (Alcohol & Diabetes; Alcohol and Dementia; Alcohol &Cancer; Alcohol and Hypertension) (Alcohol Concern, 2015b, 2015d, 2015a, 2015c)	Nov 2015	10	1	No	NA	1	1	Detailed	Alcohol Concern Lundbeck
R13	All Party Parliamentary Group on Alcohol Misuse Manifesto Report 2015 (All Party Parliamentary Group on Alcohol Misuse, 2015)	2015	10	1	No	NA	1,2,3,13	1	Detailed	Alcohol Concern (as Secretariat to APPG on Alcohol Misuse) Lundbeck
E1	Medical Council on Alcohol Annual Meeting and Symposium (Medical Council on Alcohol, 2012)	Nov 2012	1	2	No	NA	17	9	Detailed	Medical Council on Alcohol, Lundbeck (plus 7 other sponsors)
E2	Alcohol Dependence in Scotland (Powerbase, 2013)	May 2013	2,6	2	No	NA	15	6	Lacking	Lundbeck, Wellbeing Alliance, Scottish Parliament
E3	Alcohol Concern Annual Conference 2014 (Alcohol Concern, 2014a)	Nov 2014	1	2	No	NA	1,2,10	9	Detailed	Alcohol Concern Lundbeck
E4	Alcohol Concern Annual Conference 2015 (Alcohol Concenr, 2015e)	Nov 2015	1	2	No	NA	1	9	Detailed	Alcohol Concern Lundbeck
E5	Nursing Events in Practice (Nursing Events in Practice, 2015)	May 2015	1	2	No	NA	4,7,8,15	7	Some	Alcohol expert sponsored by Lundbeck

E6	HAGA Head in the Cloud: Online Brief Treatment for Alcohol in General Practice (HAGA, 2015)	May 2015	1	2	No	NA	8,14	6	Lacking	HAGA Lundbeck
E7	CRI Clinical Conference: New Trends in Addiction and Innovations in Treatment (CRI and the University of Manchester, 2015)	June 2015	1	2	Yes	1	6,7,13, 15	7,9	Some	CRI Lundbeck
E8	Medical Expert Steering Group on the Management of Alcohol Dependence (Medical Expert Steering Group on the Management of Alcohol Dependence with Lundbeck UK Ltd., 2013)	2013	10	2	No	NA	15	6	Detailed	Alcohol expert group sponsored by Lundbeck
E9	Expert meeting of Scottish GPs: "Helping the Alcohol Dependent Patient Already in Your Waiting Room"(Gordon, *no date*)	2014	2	2	Yes	1,2,4,5,6,7,8	1,6,8,12,13, 15	6	Some	Lundbeck, Clark Health Communications
E10	Expert Roundtable Meeting: Addressing alcohol misuse with a focus on managing comorbidities such as hypertension in primary care (Lundbeck Ltd.,2014d)	June 2014	1	2	No	NA	8,9,18	6	Some	Alcohol expert group sponsored by Lundbeck Munro & Forster ACP Clinical Communications Copentown SP Healthcare Consulting
E11	Secretariat for the All Party Parliamentary Group on Alcohol Misuse (UK Parliament, 2014)	Nov 2014	6	2	No	NA	13	5	Detailed	Secretariat run by Alcohol Concern Lundbeck
E12	NHS Networks - West Midlands Mental Health Commissioning Group (West Midlands Mental Health Commissioning Group Network, 2015); East Midlands Mental Health Commissioning Group (East Midlands Mental Health Transformation and Sustainability Network, 2017)	From 2015	2	2	No	NA	10,13	8	Detailed	NHS Networks Lundbeck
P1	Alcohol Harm Map (Alcohol Concern, 2012)	Oct 2012	4	3	No	NA	1	10	Detailed	Alcohol Concern Lundbeck Munro & Forster
P2	Alcohol Impact Model (NHIS Ltd, 2013)	2013	4	3	No	NA	1	11	Detailed	Lundbeck, NHiS Ltd
P3	Patient care pathways/ICP projects: (a) South Kent Coast and Thanet - Alcohol Integrated Care Pathway Specification (Kent County Council, 2014b)	2014-2015	3,4,8	3	Yes	1,2,3,5,8,9	10	10	Some (a,b,c) Detailed (d,e)	Lundbeck (a to e), Kent County Council Public Health Team (a and b), East Surrey CCG (c), Wessex

	(b) Joint working agreement between Lundbeck and Kent County Council Public Health Team (Lundbeck Ltd., 2014c) (c) Joint working agreement between Lundbeck and East Surrey CCG (Lundbeck Ltd., 2014b) to develop a local ICP for alcohol. (d) Joint Working Group with Wessex Academic Health Sciences Network, to evaluate a treatment pathway for patients with increasing/ higher risk drinking levels. (Lundbeck Ltd., 2014a) (e) An online interactive tool for commissioners to develop alcohol ICPs in their areas (Integrated Care Pathways Development Group, 2015)									Academic Health Sciences Network and University of Southampton (d), Alcohol Concern (e), Expert Group (e)
S1	Lundbeck submission to the National Assembly for Wales Health and Social Care Committee inquiry into alcohol and substance misuse (Lundbeck Ltd., 2014e)	Nov 2014	7	4	Yes	1	1,3,4,5, 8,9	NA	NA	Lundbeck
S2	Alcohol and Drug Commissioning Framework for Northern Ireland 2013-16: consultation Questionnaire (Public Health Agency and Health and Social Care Board, 2013)	Mar 2013	7	4	No	NA	6,7,10	NA	NA	Lundbeck

1. Codelists are detailed in Table 21.

6.4.3 Key stakeholders in the marketing of nalmefene

The identified promotional activities involved engagement (either directly or indirectly) with a wide variety of stakeholders, including: charities and patient groups, commissioners and health care managers, the media, patients and the general public, policy makers, regulators, prescribers and clinicians, and alcohol experts. Some of them had received funding directly from Lundbeck (Table 27), whilst others can be linked to the funded organisations. All had a potential role in facilitating the uptake of nalmefene.

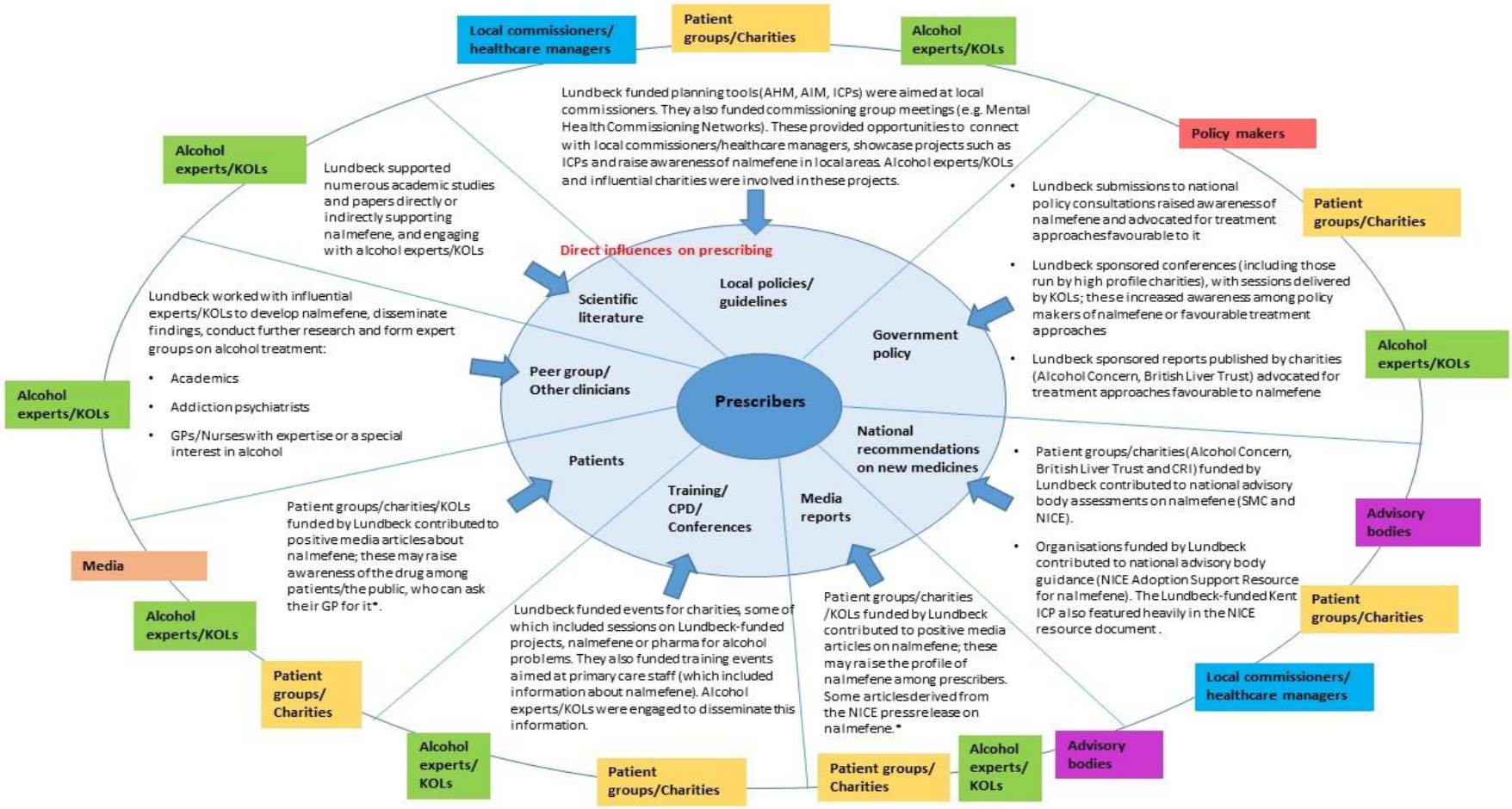
Table 27: Organisations directly supported by Lundbeck

Organisation	About	Nature of funding
Alcohol Concern	A UK charity and campaign group aiming to reduce alcohol harm (now merged with Alcohol Research UK to form Alcohol Change UK).	Annual conferences, alcohol service planning tools, joint working projects and to run the All Party Parliamentary Group on Alcohol Misuse Secretariat.
British Liver Trust	A UK liver health charity, working to improve liver health and support those affected by liver disease or cancer.	Report on alcohol treatment.
Medical Council on Alcohol	A charity aiming to improve understanding and management of alcohol-related health harm.	Conference on alcohol.
The Wellbeing Alliance Limited[1]	A consultancy involved in training, projects and research relating to improving health and wellbeing.	Lundbeck funded the Wellbeing Alliance for a UK survey about drinking habits (Mellows, 2013; Powerbase, 2014). Lundbeck also worked jointly with them on an event on Alcohol Dependence in Scotland (see Table 4 item 2).
HAGA	A local alcohol charity providing specialist support for alcohol problems	An educational event for GPs.
CRI	A national drug and alcohol charity (now known as Change Grow Live)	A conference on addiction.
Kent County Council Public Health Team	Responsible for improving the health of people living in Kent.	A joint project on ICPs for alcohol.
East Surrey CCG	Commissions healthcare for patients in East Surrey.	A joint project on ICPs for alcohol.
Wessex Academic Health Science Network (WAHSN)	One of 15 AHSNs in England, set up by NHS to drive innovation in health care; involves academic organisations, local authorities, the third sector and industry.	A joint project to evaluate a local alcohol care pathway for high-risk drinkers.
Mental Health Commissioning Networks	Regional meetings of stakeholders from primary, community, secondary care,	An unrestricted educational grant to support regional meetings

	public health, social care and third sector who are involved in commissioning and delivering services to support patient care.	

1. The Wellbeing Alliance may also have links with another charity Action on Pain, a patient group who provided a submission to the Scottish Medicines Consortium review of nalmefene. There is a footnote on an Action on Pain leaflet stating: "*Action On Pain acknowledges the kind support of the Wellbeing Alliance, a not-for-profit health consultancy, delivering evidence based campaigns across all sectors with the funding of this booklet."*

Figure 12 illustrates the potential influences on nalmefene prescribing identified from the marketing activities coded in this study. The inner circle presents a set of 'direct influences' on prescribing (for example, the scientific evidence or local guidelines). These direct influences may have been influenced by the identified marketing activities. Within each segment, Lundbeck-supported activities or organisations that have engaged with these direct influences, and which may have increased the likelihood of prescribing of nalmefene, are described. Around the outer edge of the diagram are all the identified stakeholder groups connected (either directly or indirectly) with the Lundbeck activities.



***Note that media articles were not fully examined in this study**

Figure 12: Diagram of influences, activities and stakeholders for nalmefene

6.5 Discussion

6.5.1 Summary of findings

This analysis collates and analyses diverse nalmefene promotional activities, including seeding the scientific literature with supportive articles; funding alcohol treatment reports; sponsoring events; funding alcohol service planning tools and submissions to national policy consultations. Across activities, some common themes were promoted including: claims of nalmefene efficacy and potential benefits to health and healthcare costs of its widespread adoption; increased investment in treatment; reduced-drinking interventions; greater availability of interventions for individuals without severe dependence; integrated care pathways; pharmacological interventions more generally; adherence to NICE prescribing guidelines; and a greater role for primary care in delivering alcohol interventions. A range of stakeholders were involved either directly or indirectly in facilitating or supporting the promotion including key opinion leaders (KOLs), charities and patient groups, commissioners, advisory bodies bodies and the media.

6.5.2 Promotion of nalmefene via the academic literature

Around six in ten scientific papers relating to nalmefene were sponsored by or otherwise linked with Lundbeck. This level of pharmaceutical industry involvement in the scientific literature is not unusual (Chapter 2, Section 2.3.1), and has been identified for other medicines, such as antidepressants (Ebrahim et al., 2016; Ioannidis, 2016). Clinical researchers often rotate around sectors including the pharmaceutical industry, academia and government (Marcovitch et al., 2010), a phenomenon known as ‘the revolving door’ (Meghani and Kuzma, 2011). In addition, a large proportion of health research is funded by the industry, so there is a high likelihood that clinical researchers will have received some funding from a pharmaceutical company.

The high level of involvement of Lundbeck in the nalmefene scientific literature raises questions about bias. The literature may present an overly optmistic picture of nalmefene efficacy being communicated due to the volume of supportive articles, their largely uncritical reporting and difficulty of understanding the role of Lundbeck in the papers.

Firstly, with Lundbeck support, multiple papers on the efficacy, safety and cost effectiveness of nalmefene were produced, many of these based on the same underlying patient group and covering similar themes or research questions. Publishing similar content from clinical trials

across multiple papers has been referred to as “duplicate publication” and “salami-slicing” (Ding et al., 2020) and may act to distort the medical literature by giving the impression that a drug has more support than would be warranted based on its clinical evidence (Spielmans et al., 2010). Arguably, the information reported in some of the Lundbeck-sponsored papers could have been relayed in fewer papers (although neither duplicate publication nor salami-slicing were specifically examined in this study). Lundbeck also supported other scientific papers, which, whilst not specifically about nalmefene, included nalmefene-friendly themes as outlined above.

Secondly, many academic papers presented nalmefene as efficacious but with little discussion of the limitations from the RCT data such as post-hoc sub-group analysis, as discussed in Chapter 3 (Section 3.4). Nalmefene meta-analyses with stronger links to Lundbeck were more positive in their conclusions about nalmefene than independently-conducted meta-analyses and were assessed as having a greater risk of bias (Table 24 in Section 6.4.1.3). The divergent conclusions on nalmefene may partly reflect different choices in the design, conduct and reporting of studies (including meta-analyses), some of which can work to present a drug more favourably (Lexchin et al., 2003; Prior, 2003; Ioannidis et al., 2014; Palpacuer et al., 2019). Industry-supported meta-analyses have been found to contain more methodological flaws and less detail on potential biases compared with independent meta-analyses (Jørgensen et al., 2006). This is concerning given that meta-analyses are generally thought of as the ‘gold standard’ in relation to evaluating evidence on efficacy (Forsyth et al., 2014; Ioannidis, 2016; Palpacuer et al., 2019). A recent paper has demonstrated the impact of using different inclusion/exclusion criteria and analytical models on meta-analysis results (Palpacuer et al., 2019). Vastly differing results were generated for indirect meta-analyses comparing nalmefene and naltrexone efficacy in reducing alcohol consumption, depending on the approach taken.

There was an overall positive portrayal of nalmefene in the scientific literature, regardless of COI status. Most narrative reviews of nalmefene identified in this study and elsewhere (Naudet et al., 2016a) were supportive, however not all had declared or identifiable links to Lundbeck. This may be for a number of reasons. Narrative reviews themselves may fail to critically evaluate original studies (Grant and Booth, 2009; Byrne, 2016) and in this case, broad statements about efficacy made in the original nalmefene trial papers appear to have been re-stated with little or no scrutiny. Some narrative review authors may focus on

literature which supports their own viewpoint (Grant and Booth, 2009). With nalmefene there may have been a willingness to support a new treatment option for alcohol dependence, even one which is not underpinned by strong evidence (see discussion in Chapters 7 and 8). It may be that the narrative reviews' conclusions about nalmefene were influenced by those in the original trial papers, which uncritically presented nalmefene as efficacious. This is concerning, as narrative reviews make up the bulk of the medical literature (Bastian et al., 2010) and this may have considerable influence (Baethge et al., 2019).

Although the presence of industry-related COIs in scientific papers does not imply any misconduct, these need to be made explicit and authors, journal editors and readers need to be able to recognise the potential bias arising from them. Eight of the identified papers in this study did not include any COI information at all (even just to say that there was nothing to declare), whilst two papers did not declare Lundbeck funding/links for authors that had previously been declared in other documents. Most journals request that authors disclose within the paper any information that may indicate a potential COI, but this information has often been missing or incomplete, and journals have varied in how they collect and report it (Okike et al., 2009; Forsyth et al., 2014; Shawwa et al., 2016). Improvements to disclosure policies in medical journals have been introduced, for example, aiming to standardise the COI information collected and presented across different journals (ICMJE, 2019). Problems remain, however, in understanding and interpreting the rules and definitions used, with some journals not following the recommendations fully (Dal-Ré and Marušić, 2018; Taichman et al., 2020). Readers and reviewers of scientific evidence need to be aware of COIs, and appropriately skilled to critically appraise the evidence presented (Marcovitch et al., 2010).

Taking the scientific literature analysed as a whole, readers may interpret the evidence presented as providing a general consensus about the potential benefits of nalmefene. As well as legitimising the claims made about a drug, such consensus can influence guidelines for clinical practice (Spielmans, 2015; Hastings and de Andrade, 2016). It is not only research outcomes but whole research agendas that can be influenced by industry sponsorship of research. Corporate sponsors can frame the purpose of research studies and the way that research questions are asked in a way that aligns with their commercial interests, and which steers the research agenda away from other public health interventions or topics which may not offer any commercial gain (Fabbri et al., 2018b). Through their support for the scientific literature, Lundbeck may have influenced the research agenda on solutions to addressing

alcohol harms, raising the profile of both nalmefene and pharmacological approaches more generally as solutions.

6.5.3 Promotion of nalmefene via other activities

An increasing network of stakeholders have influence over healthcare decision-making (Meyer and Müller, 2006; Pesse et al., 2006). Engaging with them can offer pharmaceutical companies opportunities to promote the use of their products (Rothman et al., 2011; Edgar, 2013). The Lundbeck-funded alcohol-related activities identified in this study allowed the company to generate relationships with many influential stakeholders (Figure 12).

6.5.3.1 Engaging with patient groups and charities

Lundbeck's engagement with national alcohol charities and patient groups included funding alcohol reports, events, and specific alcohol-related projects. Although it is difficult to ascertain the level of influence this funding had on nalmefene uptake, it was directed towards activities that could support nalmefene in some way. For example, the funding given to Alcohol Concern enabled the charity to improve its support around alcohol treatment. Earlier Lundbeck-funded charity reports (see Table 26) may have helped prepare the ground for nalmefene, for example, by raising awareness of harmful drinking and related gaps in the current treatment system.

Nalmefene-friendly messages may have been enhanced because they were delivered through charities or patient groups. The influence and reputation of these groups makes them attractive partners for pharmaceutical companies; they have a say in public and policy debates about drug availability and prescribing (Buttle and Boldrini, 2001; Rothman et al., 2011; Edgar, 2013), described as 'grassroots lobbying muscle' (Burton and Rowell, 2003). They can act as 'third-party' communicators, through which pharma-friendly messages can be delivered, and in a way which is perceived to be more independent and credible than those delivered directly by a pharmaceutical company (Rothman et al., 2011).

Charities and patient groups are routinely consulted in regulatory assessments of new drugs (Colombo et al., 2012; Mandeville et al., 2019), and Lundbeck-funded charities participated in national advisory body assessments of nalmefene (Scottish Medicines Consortium, 2013; NICE, 2014c, 2014d, 2014e). Their statements indicated support for the drug (NICE, 2014d,

2014e), which is consistent with other research (Lexchin, 2019). Lundbeck-funded charities also contributed supportive statements to news articles about the benefits of nalmefene (Ross, 2013; Smith, 2014). There is no indication from this study that such support was a condition of the Lundbeck funding. However, it is possible that organisations or individuals receiving industry funding may be influenced in subtle ways that they may not even be aware of (Dana, 2003; Bhattacharyya and Benbow, 2018). Furthermore, research suggests that receipt of gifts or funding, even of small amounts, can generate a reciprocal response among recipients (Katz et al., 2003; Association of American Medical Colleges and Baylor College of Medicine, 2007).

However insufficient as a measure for addressing COIs (Loewenstein et al., 2011), industry links should at least be clearly disclosed in regulatory or official processes. It is not clear from this study how disclosure of Lundbeck funding was made by the charities when they contributed supportive statements on nalmefene to the NICE TA assessment. However, in the two statements examined, only one contained any mention of Lundbeck funding (NICE, 2014d, 2014e), although it is possible that funding was disclosed in other documents not obtained in this study. Industry links may be less transparent in other activities; funded organisations' links to Lundbeck were not stated in some media articles (Ross, 2013; Smith, 2014).

Pharmaceutical industry funding of charities and patient groups appears to be increasing (Ozieranski et al., 2019) while disclosure policies for these organisations are weak, culminating in limited or low levels of reporting of industry payments, making it challenging for others to be made aware of industry links (Rothman et al., 2011; Ozieranski et al., 2019; Rickard et al., 2019). Stronger policies for all organisations contributing to policy, regulatory and media activities have been requested (Rothman et al., 2011; Mandeville et al., 2019). Organisations making submissions to NICE assessments are required to declare their interest, including "*funding received from the manufacturer of the technology*" although this only relates to the previous twelve months (NICE, 2019, p. 13). However, many of the potential conflicts of interests among patient groups submitting to NICE assessments may be unknown to NICE decision-making commmittees, suggesting that the disclosure policy is insufficient in identifying all relevant interests among patient groups (Mandeville et al., 2019). COIs among organisations commenting in media articles, however, tend to go undisclosed (Cook et

al., 2007), which raises concerns given the potential influence these media reports can have on the public (Henderson and Hilton, 2018).

Funding of charities has the potential to bias the focus of the charities in favour of commercial interests (Ozieranski et al., 2019). Charities have faced cuts in government funding and some of them may feel pressure to focus attention towards funded topics and policies rather than advocating for other approaches (Baggott and Jones, 2015). Only organisations or issues that align with private funders' interests may be given a voice (Batt, 2014; Baggott and Jones, 2015), prompting calls for reforms to the way patient organisations are funded and their COIs managed (Rickard et al., 2019).

6.5.3.2 Engaging with national and local policy makers

Lundbeck also directly engaged policy makers at both national and local level, including making submissions to national policy consultations about alcohol. Lundbeck raised similar themes discussed earlier: building knowledge awareness of nalmefene and advocating for increased treatment provision and interventions to reduce alcohol consumption. As with other funded activities, there is a risk of agenda-shift, where the focus is on policies favourable to industry, at the cost of other approaches. This has been observed in relation to the alcohol industry, where efforts have been directed towards shifting agendas away from policies addressing alcohol harms at the population level to those which focus on smaller sub-populations (McCambridge et al., 2014).

Lundbeck engaged with local healthcare commissioners and managers (including CCGs) responsible for alcohol treatment services. Working jointly with commissioners on the development of ICPs may have given Lundbeck the opportunity to help shape how services are delivered, including nalmefene treatment. ICPs facilitate patient group identification and access to treatment (Baxter et al., 2018), an aim likely shared by local alcohol commissioners and Lundbeck. The exact details of Lundbeck's joint work with commissioners on ICPs has not been obtained. However, their involvement raises questions about potential bias, which may have worked in subtle ways to benefit nalmefene. For example, the Kent ICP specification document (Kent County Council, 2014b) contained numerous references to nalmefene and products or resources linked to the drug company.

Whilst Lundbeck involvement in the ICP work was disclosed in documents directly relating to the project, the link is not explicit in other documents. For example, the Lundbeck-funded

ICP work featured heavily in the NICE 'Adoption support resource – insights from the NHS' document for nalmefene (NICE, 2015). The Lundbeck-funded Kent ICP is included as an example of how nalmefene has been implemented; no mention is made in the document of Lundbeck's involvement in funding this. Neither is Lundbeck mentioned by name in relation to their funding of organisations and individuals who contributed to the Adoption Support Resource document. Instead, the document[22] includes a statement that the sites involved in the development of the document have received "*honoraria, support or funding in part from the company*" (NICE, 2015, p. 20). In England, pharmaceutical funding to CCGs has tended to focus on sponsorship of educational or training events, with around a fifth going towards specific projects, some with links to company's product; a large number of these payments have not been disclosed (Moberly, 2018). Policies on acceptance and disclosure of payments have differed across CCGs, with some deciding against any payments in order to avoid any undue bias in decision-making (Moberly, 2018).

6.5.3.3 Engaging with experts, clinicians and prescribers

Lundbeck have engaged directly with alcohol experts and prescribers through a range of funded activities including conferences, educational events and expert meetings, increasing awareness of nalmefene among individuals who could then go on to influence their peers. Their involvement of KOLs (Burton and Rowell, 2003; Moynihan, 2008) can influence not only clinical practice but also research agendas and policy debates (Prosser et al., 2003; Meffert, 2009; Alves et al., 2019). As with patient organisations, the messages they relay are perceived to be independent and therefore more credible (Burton and Rowell, 2003). In this case, these activities are likely to have acted to strengthen support for nalmefene.

6.5.4 Transparency and beyond

Lundbeck's involvement was not always clearly stated in journal articles supporting the drug nor in stakeholder activities, including those which feed into national guidance for nalmefene (the NICE Adoption Support Resource)(NICE, 2015). It is concerning when public and professional stakeholders are presented with information or recommendations that do not clearly disclose the involvement of organisations who stand to gain or lose. Whilst journal

[22] This document can now only be obtained online via archived pages on the Wayback Machine, but only some pages are available. A full pdf of the document is available on request.

editors, advisory bodies and health care organisations need to be more vigilant about COIs, greater transparency is not a complete solution as it will not address the risk of bias and agenda shift which may be generated by the involvement of private industry in research and in the work of stakeholder groups (Cain et al., 2005; Fabbri et al., 2018b). Other approaches to addressing or preventing alcohol problems (including non-pharmacological or population-wide measures) may be given less weight in both the evidence base and in wider debates. This conflicts with international evidence and recommendations finding that whilst targeted interventions for alcohol treatment have a place, population measures are the most effective in reducing alcohol harms (Babor et al., 2010; University of Stirling, 2013; WHO, 2018a). Alternative funding arrangements and models of working that may help facilitate more independence in health research, education and clinical practice are already being discussed (Moynihan et al., 2019).

6.5.5 Strengths and limitations

Key strengths of this study are the breadth of activities included, clear descriptions of the steps used to identify and analyse documents, a risk of bias assessment of meta-analyses checked by a second researcher, and an independent review of the analysis of a sample of scientific papers and 'grey' literature. Further, the documents have been made publically available online: web links, including those obtained via the 'Wayback Machine' (*The Wayback Machine,* no date) have been provided where documents can still be accessed online.

However, the analysis is subject to at least five key limitations. Firstly, the analysis was limited to scientific papers identified in a systematic literature search which included search terms relating to 'nalmefene', was limited to papers published between 2010 and 2017 and excluded numerous editorials, commentaries and conference abstracts (see Chapter 3, Figure 1). The full text for six scientific papers was not obtained after efforts to contact authors and to obtain these via the University of Stirling library. There are therefore likely to be other scientific papers funded by Lundbeck, not considered here and the influence of Lundbeck on the scientific literature may be underestimated. Secondly, some limitations were placed on the scope of the analysis of the scientific literature due to time constraints. The numerous editorials, commentaries and conference abstracts identified, all potential vehicles for promoting nalmefene, were excluded. No overall comparative analysis of independent versus Lundbeck-affiliated research on nalmefene was conducted. Comparisons were made in

relation to narrative review papers (comparing the number supporting nalmefene by COI status) and meta-analysis papers (comparing overall conclusions on nalmefene beween the Lundbeck-supported and independent meta-analyses). It was not possible to compare other groups of papers (original trials, secondary analyses, papers on alcohol treatment) in this way as Lundbeck were involved in all of the papers identified. Finally, a risk of bias assessment was not conducted on papers other than meta-analyses, meaning that comparisons of risk of bias between Lundbeck-funded and other systematic reviews without meta analysis cannot be reported. Thirdly, Lundbeck-funded activities for which there is no online record or where funding was not acknowledged will have been missed from this analysis, which therefore likely represents a subset of all relevant marketing activity. Fourthly, media reports (which may be considered part of the marketing of a drug) were not analysed. Finally, some documents relating to Lundbeck-funded activities were difficult to find online as they had been removed from various organisational websites and had to be sourced using the 'Wayback Machine' which archives webpages. Nonetheless, the archived information did not always provide the full text for some documents which may have limited the analysis.

Despite these limitations, the documents obtained illustrate the rich variety of activities and stakeholders involved in the promotion of nalmefene, and provide a level of detail which participants in the qualitative phase of the study may be unable to recall.

6.5.6 Conclusion

This documentary analysis study found that the pharmaceutical company responsible for promoting nalmefene (Lundbeck) implemented a large programme of promotional activities for nalmefene which created opportunities to influence the uptake of nalmefene in UK alcohol treatment. Their support generated a large number of supportive academic papers relating to nalmefene and re-emphasises doubts about the ability of the system of peer-review and evidence-based medicine to withstand commercial influence (Moynihan et al., 2019). Their funding of a range of influential organisations and associated activities (including their involvement in alcohol treatment recommendations and care pathways) may have worked in subtle ways to influence conditions favourable to nalmefene prescribing. It is not clear from this analysis why the efforts made by Lundbeck were ultimately unsuccessful in generating high levels of prescribing for nalmefene as reported earlier (Chapter 5 on nalmefene prescribing). This will be further analysed in qualitative interviews with key professionals working in alcohol treatment (Chapter 7).

7 STUDY 3: KEY STAKEHOLDERS' VIEWS ON NALMEFENE: A QUALITATIVE ANALYSIS

7.1 Introduction

This chapter presents an analysis of the semi-structured interviews conducted with key stakeholders, providing qualitative insights on nalmefene, its licensing conditions and the findings previously discussed in Chapters 5 and 6 on its use in primary care and its promotion. Participants were asked to reflect on questions identified from these earlier stages of the study, including their views on the evidence, possible explanations for prescribing patterns, 'real-world' accounts of how they have prescribed nalmefene, and experiences and views about how it was promoted. The study aims and objectives are outlined first, followed by the methods used and the results obtained. The results are discussed, drawing on the wider literature, followed by a consideration of the study strengths and limitations and a conclusion.

7.2 Aims and Objectives

The aim of conducting these interviews was to understand how nalmefene was used in UK primary care and factors influencing its use, from the perspectives of a variety of stakeholders involved in addressing alcohol problems. The objectives were to:

- understand how key stakeholders view nalmefene and its licensing conditions;
- gain insights into experiences of how nalmefene has been used in the UK (including individual prescribing experiences), perspectives on the prescribing patterns observed in the quantitative analysis, and factors perceived to have influenced uptake); and
- understand how key stakeholders experienced nalmefene promotional activities, and their perceptions of how successful these were.

7.3 Method

7.3.1 Rationale for the approach

Qualitative methods can facilitate an in-depth understanding of phenomena, behaviours and processes (Mason, 2002; Bryman, 2004; Creswell, 2007). A qualitative approach was therefore appropriate to obtain a deeper understanding of nalmefene and how it has been used in UK primary care. It allows the research to focus on the perspective of the participant

(Creswell, 2007), and how they understand certain phenomena in their own social world (Ormston et al., 2014). This phase of the study used semi-structured interviews with a range of professionals whose work involved addressing alcohol problems. This offered valuable insights about nalmefene based on 'real-world' knowledge, processes, experiences and attitudes.

This study used semi-structured interviews, which were based on a topic guide outlining the themes to be covered, and allowing important questions to be addressed, whilst at the same time offering flexibility to probe responses for more detail and to cover additional and unanticipated material that was important to the participant (Sarantakos, 1998; Bryman, 2004). This was particularly useful to my study, as I had no prior expertise in alcohol treatment or nalmefene and may not have anticipated some of the important issues to understanding nalmefene. Individual interviews rather than focus groups were selected to enable participants to articulate their own perspectives about nalmefene in confidence. Participants are less likely to feel comfortable expressing attitudes that may be controversial or in disagreement with mainstream views in focus group settings (Finch et al., 2014).

7.3.2 Sampling

I aimed to interview 25 individuals, ideally spread across the UK, who have expertise or knowledge of nalmefene, experience of prescribing it to patients, or experience or awareness of how it was marketed. The inclusion criteria were wide, including those with national-level (for example, alcohol experts or those working in alcohol policy), local-level (for example, local commissioners or people with influence over local prescribing) and individual-level (GPs, psychiatrists, specialist alcohol staff) perspectives. Of these 25 participants, the aim was that at around ten would have nalmefene prescribing experience, half of whom were GPs. In selecting individuals to approach for interview, an effort was made to obtain a variety of perspectives by including both those more likely to be supporters, and those more likely to be critics of nalmefene. This was achieved based on known information about participants, such as that they had worked with Lundbeck on nalmefene, or had written papers either supporting or criticising the drug.

Potential participants were identified using purposive sampling, which has been described as *"non-random ways of ensuring that particular categories of cases within a sampling universe are represented in the final sample of a project"* (Robinson, 2014, p. 32). The approach has been used widely in qualitative research where there is a need to identify and select

individuals with expertise in the topic being studied (Creswell and Plano Clark, 2011). The approaches used to identify participants in this study included scanning the authorship of published papers on nalmefene (Chapter 3), reviewing materials gathered for the documentary analysis of nalmefene marketing (Chapter 6), and using contacts gathered during earlier scoping work. A 'snowball sampling' (Robinson, 2014) technique was also used, where recruited participants were asked to recommend colleagues who were potentially eligible to participate in the study and either provided the researcher with names of colleagues to contact or provided colleagues with the researcher's details and a summary of the study, or both.

7.3.3 Ethics and other approvals

Ethical approval for this study was granted by the University of Stirling NHS, Invasive or Clinical Research (NICR) Committee (NICR 18/19 – Paper No. 033). NHS Research Ethics Committee approval was not required, however, local NHS Research & Development (NHS R&D) co-ordinators were informed about the study as a courtesy, in advance of interviewing any individuals in their area who were working in the NHS[23]; the replies received indicated that no NHS R&D approval was required.

7.3.4 Recruitment and consent

Potential interviewees were emailed to check their willingness to participate in the study. A reminder email was sent to those who had not replied after two weeks, and a final reminder was sent to a small number who had not replied after three weeks.

Eligible participants were emailed information about the study and invited to participate. The email requested that they read two attached documents – a Participant Information Sheet (PIS) and a Consent Form. The PIS included information on the study background and aims, its voluntary nature, and what would be involved in taking part. An explanation of the process for data storage and protecting participant anonymity was also included (Appendix 4). My contact details were provided in the email and PIS document for participants who wished to discuss the study. Participants were asked to sign and return the Consent Form if

[23] Information about the study was sent to the NHS R&D co-ordinators in 4 areas: Grampian, Greater Glasgow and Clyde, Lothian, and South London and Maudsley.

they wished to participate (Appendix 4). This included consent for recording and transcribing the interview, which was re-confirmed with participants at the start of their interview.

Participants who agreed to be interviewed were emailed a table of potential dates and times for interview, and were asked to indicate which were suitable. They were re-contacted by email to confirm the date and time for their interview.

7.3.5 Data collection and management

Semi-structured interviews were conducted with the aid of a topic guide (Appendix 4) covering the following key areas:

- Participant role and background;
- Experience of nalmefene;
- Views about nalmefene and its licensing conditions;
- Experience of prescribing nalmefene (if appropriate);
- Views about prescribing levels in the UK and what factors have influenced these;
- Experience and views about nalmefene promotional activities organised by Lundbeck, the drug company who market nalmefene.

The topic guide was informed by earlier phases of the study, including the nalmefene literature (Chapter 3) and the prescribing data analysis (Chapter 5). It was also refined at various points during the qualitative fieldwork to take account of new lines of questioning raised in earlier interviews. The researcher wrote up summary notes immediately after each interview, and reviewed the topic guide before the next scheduled interview.

One interview was carried out face-to-face in the participant's workplace, and 18 were performed by telephone. Interviews were conducted between March and April 2019, lasted between 27 and 55 minutes (mean=39; median=38) in length, and were recorded using a digital audio recorder. Audio recordings were downloaded to a secure password-protected folder on a university server, after which they were deleted from the digital recorder. They were transcribed by a professional transcriber, with the resulting transcriptions saved securely in a password-protected file, accessible only to my academic supervisors and me. I then

reviewed all transcriptions alongside the audio recordings to check the quality of the transcribed data, to ensure that identifying data were removed, and to address, as far as possible, any amendments needed due to transcriber error or poor audio quality.

All participants had an opportunity to review their transcript for completeness and accuracy and to highlight content which they felt could potentially risk disclosing their identity if used in quotes. An encrypted transcript file was emailed to each participant to review. Five participants took up this offer. Of these, four returned an annotated copy of their transcript, addressing specific queries that I had highlighted, whilst one got in touch by phone to clarify these queries.

Participants were referred to by using an ID code in all audio recordings, transcripts, notes and analysis files. The ID codes assigned to individuals were stored in a secure folder, separate from any data or analysis files.

7.3.6 Data analysis

A thematic approach was used for data analysis. This identifies and analyses qualitative data around patterns of meaning (themes) (Clarke and Braun, 2014). The data were organised and analysed using the Framework method (Spencer et al., 2014), in which qualitative data are summarised and organised using a matrix, allowing analysis by themes and by cases. Seven stages are involved: transcription of the interview data; familiarisation with the interview data; data coding; developing a working analytical framework; applying the analytical framework; charting the data; and data interpretation (Gale et al., 2013). The Framework approach offers a systematic, comprehensive and transparent method of analysing qualitative data (Ritchie et al., 2014a).

Familiarity with the qualitative data was obtained through reading transcripts and researcher notes and listening to the audio files. Topics emerging from the transcripts were listed, and then grouped into a set of initial themes and sub-themes. These themes formed the initial code frame for sorting the data, allowing data which is similar or about the same theme to be grouped together, a process referred to as ‘indexing and sorting’ (Spencer et al., 2014). The code frame was continually revised to capture new themes emerging from the transcripts, or to merge or split themes to more accurately represent the data. Data from each interview transcript were coded against these themes and sub-themes. Once coding was complete, a series of matrices representing the themes and sub-themes were created. Data grouped under

each sub-theme were then summarised and added into the matrix for each participant, including some illustrative quotes. The final matrix comprised six matrices, all of which had a number of sub-themes (see Appendix 5 for the final framework matrix).

These data summaries were analysed by theme to provide a descriptive account of participants' views. This involved going back to the indexed raw data where necessary to check on assumptions and interpretations. The summaries were also analysed to look for patterns of association or 'linkages' across the data for an individual participant – to see how the data 'hang together', as described by Dey (1993). I also explored whether certain views expressed in the data were linked to whether participants had worked with the drug company.

The qualitative analysis software NVivo Version 11 (released 2015)(QSR International Pty Ltd., 2015) was used to manage the data and produce the framework matrix.

7.4 Results

In all, 36 potential interviewees were approached to participate in the study. Seventeen of those approached did not participate, either because they declined (*n*=7) or did not reply to any of the email requests (*n*=10). Reasons given for declining included insufficient knowledge of nalmefene (*n*=4), being too busy (*n*=1), or simply that they were unable to participate (*n*=2). Of those who declined or failed to reply, seven of 17 had, to the best of my knowledge, conducted some work with Lundbeck on either nalmefene or alcohol-related projects.

The results are described under five headings, aligning closely with the broad categories in the topic guide and the final matrix (Appendix 4 and 5). Section 7.4.1 outlines participant characteristics and briefly summarises their nalmefene experience, while Sections 7.4.2 to 7.4.5 discuss participant views about nalmefene, their prescribing experiences, perceived influences on prescribing nalmefene, and, finally, their experiences and views on the marketing of nalmefene.

7.4.1 Participant characteristics and experience of nalmefene

Of the 19 participants, 15 had clinical expertise in alcohol treatment. Most of these worked in psychiatry (*n*=11), a further two were alcohol specialist nurses, one was a GP, and one a pharmacist. Of the four participants with no specialist clinical expertise in alcohol treatment, two were working, or had worked, in local alcohol services commissioning, one was an

experienced general practitioner now working in academic health research, and one was previously a GP but now working in a public health policy role. Ten participants were currently working in Scotland and nine in England (Table 28). The country in which participants work is not displayed in Table 1 due to the risk of disclosing their identity.

Twelve participants had prescribed nalmefene to patients (7 of whom had also previously worked with Lundbeck on nalmefene). Of the five non-prescribers, one had been involved in Lundbeck work on nalmefene, whilst others had gained familiarity with nalmefene via contacts from Lundbeck, from attending conferences, or from colleagues who had links with Lundbeck.

Table 28: Participant characteristics

ID	Current Role	Professional background	Expertise in alcohol treatment	Setting	Prescribed nalmefene	Worked with Lundbeck on nalmefene[1]
1	Policy role	Nursing	Yes	Policy/previously NHS/Charity sector	Yes	No
2	GP	General Practice	Yes	NHS	Yes	Yes
3	Consultant Psychiatrist	Psychiatry	Yes	Other/previously NHS	Yes	Yes
4	Consultant Psychiatrist	Psychiatry/General Practice/Commissioning	Yes	NHS	Yes	No
5	Alcohol policy	Alcohol services/Commissioning	No	Other	No	No
6	Pharmacist	Pharmacy	Yes	NHS	Yes	No
7	Consultant Psychiatrist	Psychiatry	Yes	NHS	No	No
8	Consultant Psychiatrist	Psychiatry	Yes	Third sector	Yes	Yes[2]
9	Consultant Addiction Psychiatrist	Psychiatry	Yes	NHS	Yes	Yes
10	Consultant Addiction Psychiatrist	Psychiatry	Yes	NHS	No	No
11	Policy role	Psychiatry	Yes	Other/previously NHS	No	No
12	Consultant Psychiatrist	Psychiatry	Yes	Other/previously NHS	Yes	Yes
13	Alcohol Strategy Lead/ Commissioner of Services	Alcohol Services/Commissioning	No	Local Council	No	No
14	Academic/Addiction Psychiatrist	Psychiatry	Yes	Academic NHS	Yes	Yes
15	Public Health	General Practice/ Alcohol policy	No	NHS	No	No
16	Consultant Addiction Psychiatrist	Psychiatry	Yes	NHS	Yes	No
17	Consultant Addiction Psychiatrist	Psychiatry	Yes	NHS	Yes	No
18	Academic	Academic/General Practice	No	Academic	No	Yes
19	Academic/Nursing	Academic/Nursing	Yes	Academic/NHS	Yes	Yes

1. Includes: chairing meetings, conference presentations, consultancy and project work and involves some remuneration.
2. This participant chaired a session at a conference and did indicated that this did not involve any fees.

7.4.2 Views about the value of nalmefene and its licensing conditions

Nalmefene was viewed by some participants as a potentially valuable new treatment in that it was targeting a group of drinkers whose needs were "*not well-served by current treatment models*" (ID1, Nursing). It was viewed as being a potential way of engaging this neglected group of patients with treatment, or at least to initiate discussion about their alcohol problems. A number of features were thought to be appealing to patients: they could be treated in primary care rather than have to attend a specialist service; because nalmefene could offer some control or "*ownership*" (ID12, Psychiatry) over their alcohol problem due to its 'as-needed' regimen (rather than having to use it daily); and it would offer the option of cutting down their drinking as opposed to stopping drinking immediately.

Having an additional alcohol treatment option was considered valuable in itself, a theme raised by many participants. Linked to this, there was support among some participants for a variety of approaches to be available to address the heterogeneity in alcohol problems. In this sense it was felt that nalmefene may be of benefit to some individuals:

> *… there's a million and one routes to recovery. And some people's route to recovery may be, actually I just need to take a pill before I drink*. (ID16, Psychiatry)

> *… with certain selected groups, actually it's a very worthwhile intervention. (ID12, Psychiatry)*

Participants described scenarios where they felt nalmefene could be valuable: managing patients before they got to the dependence stage; providing an alternative option when other medicines (for example, naltrexone) are unsuitable; helping binge drinkers to cut down their drinking; and helping patients who have relapsed when trying to aim for abstinence, with nalmefene helping to "*transition*" (ID14, Psychiatry) patients from reducing to stopping drinking altogether.

However, despite seeing the potential advantages of having another treatment option to offer patients, many participants voiced concerns about aspects of the nalmefene evidence that raised doubts about its value in treating alcohol problems (discussed further in Section 7.4.4.4).

7.4.3 Prescribing experiences

Although some of the participants were clinicians, they had limited experience with prescribing nalmefene. In some areas (in Scotland and England), it was not on the local drug formulary and some participants were unaware of any nalmefene patients in their local service. The general perception was that the drug was not widely used in the UK. Those who had prescribed nalmefene (*n*=12) reported that it was prescribed to a small but diverse group of patients with alcohol problems – *"a mixed bag"* (ID12, Psychiatry), ranging from those without alcohol dependence to those with severe alcohol problems and dependence. (For information here, the conditions applying to nalmefene's license are shown in Box 2).

Box 2: Nalmefene licensing conditions

Nalmefene is licensed for the reduction of alcohol consumption in the following patients:

patients with alcohol dependence;

who are drinking at a high drinking risk level (DRL)(more than 60g alcohol per day in men and more than 40g alcohol per day in women);

and without physical withdrawal symptoms and who do not need immediate detoxification.

It should only be given to patients who continue to drink at a high DRL 2 weeks after an initial assessment.

It should only be given in conjunction with continuous psychosocial support focused on treatment adherence and reduction of alcohol consumption.

As noted in Box 2, nalmefene should be prescribed to patients with alcohol dependence who are not experiencing withdrawal symptoms. However, some participants (all from specialist services) expressed divergent views on prescribing it to patients with alcohol dependence, due to a risk of withdrawal symptoms in these patients. One felt comfortable prescribing to patients with severe levels of dependence because he could monitor them himself for signs of alcohol withdrawal. Some others had concerns about prescribing to individuals diagnosed with any level of alcohol dependence. One would only prescribe to binge drinkers able to sustain some "*dry days*" (ID8, Psychiatry), adding that "*if there is any whiff of dependence I will not go to nalmefene*" (ID8, Psychiatry). Another was concerned that, because patients often underplay their drinking, this meant there was uncertainty about their risk of withdrawal symptoms – "*so can you be fairly sure they are in this mild 'not at risk of withdrawal' category?*" (ID9, Psychiatry).

The nalmefene patients described by participants had varying levels of previous contact with alcohol treatment services. Some were described as "*experienced*" (ID3, Psychiatry) patients, having tried other options and being keen to try something new – "*they would grasp at any whisper out there of another method*" (ID3, Psychiatry). Others were described as being more unusual – *"not the normal sort of clients we'd see*" (ID12, Psychiatry), well-educated and well-informed individuals who had "*done their research*" (ID4, Psychiatry). In this sense, it was felt by some participants that nalmefene may have "*opened up the service to people who might not have accessed it before*" (ID17, Psychiatry).

Some limited information about patient experiences of nalmefene was collected, although it was difficult for participants to recall the details. One participant (from primary care) also added that it was difficult to know whether nalmefene had helped, as most of his patients had not returned after one prescription. Where details were given, these suggest a mix of patient experiences. Some participants recalled that a few of their patients who had been prescribed nalmefene had been able to reduce their drinking, but that it didn't work for all – "*And I think one or two, no more than three or four other patients who similarly were aware that their consumption had gone down by a third to a half*" (ID9, Psychiatry).

A few participants reported that many of their patients received only one prescription of nalmefene – "*I don't think anyone got more than one prescription*" (ID2, General Practice). Some possible explanations were offered. A few participants reported that many patients experienced strong side effects whilst on the drug, which were "*intolerable*" (ID17, Psychiatry) and acted to deter patients from using the drug: "*it makes them feel very out of control, they feel like they are not in their own body and they really disliked the feeling and just can't take it. That's not uncommon*" (ID19, Academic/Nursing). Several participants recalled that patients either did not respond or that they had been disappointed in the effect of the drug: "*instead of having eight drinks they had six drinks, I mean it's not that striking*" (ID2, General Practice). It was also suggested by some of participants that one prescription of tablets may have lasted a patient a considerable length of time, assuming they were not used daily; one of these participants implies that nalmefene could be prescribed to patients drinking once or twice a week – "*if you think about it, it was meant for someone who was drinking once or twice a week to excess. A 28-day supply will give you a lot, it'll give you six-months or something, won't it?*" (ID16, Psychiatry).

Different models of nalmefene delivery were described by participants. In some areas, primary care physicians could prescribe it; in others, it had to be prescribed or, at least, initiated, by specialist services. Other areas used a 'shared care' model, where specialist services staff were embedded within a GP practice, and in two areas only hospital-based alcohol teams were allowed to prescribe nalmefene. Even within a single CCG area in England, there could be different policies:

> *… we actually have three therapeutic prescribing committees in my patch, and I think two of them said they wouldn't prescribe it even though it was obviously approved by the NICE technology appraisal, but one area said they would.* (ID12, Psychiatry)

Participants reported that a variety of packages of psychosocial support were offered to patients prescribed with nalmefene, ranging from a series of structured psychosocial support sessions delivered by specialist services staff or a shared care worker situated in a GP practice to online psychosocial support programmes. Online programmes were thought to be increasingly popular and viewed as being useful for patients with mild dependency, and in areas where the only alternative would have been for patients to attend a local drug service. One GP participant commented that patients may engage in different forms of psychosocial support, and that he may not know whether they were regularly attending some of these.

7.4.4 Influences on nalmefene prescribing

From participant accounts, a broad range of factors may have influenced nalmefene prescribing (the influence of marketing activities undertaken by the drug company are discussed in Section 7.4.5). These included: a general willingness to support new treatment options; an endorsement from NICE; the media; the RCT evidence on nalmefene; perspectives about the use of naltrexone for reducing alcohol consumption; the nalmefene licensing conditions; the current alcohol treatment system; and beliefs and attitudes about alcohol problems and treatment. These are now discussed.

7.4.4.1 "Another tool in the toolkit"

Participants wanted more options for treating individuals with alcohol problems, and supported nalmefene for that reason:

> *So for me I was quite excited and thought it was really worth … promoting and giving another tool in the toolkit for GPs and especially managing people before they got to the dependence stage. I was very keen for it to be licenced … well, on the formulary.*
> (ID4, Psychiatry)

There was still some enthusiasm for a new treatment, even when participants were not wholly convinced by the evidence:

> *But I then I remember just feeling it's not the best trial design. Where I come from here, is there is such a paucity of anything for people who have developed an alcohol use disorder of any sort, so anything additional is a positive. We have a very small toolbox in this field and I just think if anything can add and improve our outcomes then I'm really willing to give it a go.* (ID19, Academic/Nursing)

7.4.4.2 Endorsement from NICE

The endorsement of nalmefene by the UK National Institute for Health and Care Excellence (NICE) was seen as being influential in establishing the drug in some local areas – "*it gets attention*" (ID1, Nursing). Another described how this endorsement was used by drug company reps in their promotion of the drug –"*was really trying to capitalise it seemed on this kind of NICE endorsement as it were*" (ID5, Alcohol Services/Commissioning). The stronger obligation placed on NHS services to provide medicines that have been recommended in NICE Technology Appraisals (TA) (as with nalmefene) was mentioned by two of the participants, including the legal requirement within it:

> *… a guideline is a guideline, it can be followed but it doesn't have to be followed. If something is approved by a Technology Appraisal, if you go to the NICE's website and look up the wording, is by law, and it only applies to England obviously, not Scotland, but the Secretary of State by law says this has to be made available if someone wants it*. (ID16, Psychiatry)

One participant described his and his colleagues' surprise that nalmefene had been endorsed by a NICE TA:

> *But I think people were shocked at that, you know. I think people said, 'How the hell did they manage to get that?' And you have to look at the whole, kind of … because I think, and I presume you have looked at the evidence-base …* (ID16, Psychiatry)

7.4.4.3 The media

Many participants commented that there had been a high level of media coverage of nalmefene, which had presented the drug as a valuable addition to treatment – "*I think some of the papers were saying it was the new cure for alcohol problems*" (ID12, Psychiatry). This was said to have increased public awareness of the drug, prompting some to go to their GPs for it. The media coverage also created pressure to provide nalmefene in some areas:

> *I feel like around whenever the drug was released … it was heavily promoted in the media and I almost feel like if the health board had have said 'no' there might have been a bit of … almost uproar because they have such a big alcohol problem.* (ID6, Pharmacy)

One participant likened the media coverage to a form of "*direct marketing*" (ID10, Psychiatry). Others commented that it was unusual – "*I've never seen a promotion quite like it actually*" (ID17, Psychiatry), or queried where the media articles came from: "*there were articles appeared in the Daily Mail about it. Which I, you know, I don't really understand where or how those articles came from and how they didn't constitute advertising, but who knows?*" (ID16).

7.4.4.4 The nalmefene evidence

Many participants talked about having a lack of faith in the evidence from the nalmefene clinical trials, which had discouraged the use of the drug. One described a "*lack of clarity*" around the evidence that made people feel "*cynical*" (ID12, Psychiatry) about its proposed benefits. Problematic issues that were raised included the small effect size for nalmefene in reducing alcohol consumption compared with a placebo treatment, described by one participant as: "*not a game changer*" (ID1, Nursing). Another participant felt that the evidence from the trials may have been over-interpreted:

> *But there was quite a controversy about the claims that were made, for the size and nature of the effects. And I think there were probably too few well-*

designed studies and over-interpretation of the findings of those studies.
(ID18, Academic/General Practice)

Other issues raised included that the results were based on a sub-sample of the original trial population rather than the whole trial population, and that there was potential bias, as the trials were "*all company-sponsored*" (ID17, Psychiatry). The applicability of the evidence to drinkers in the UK was also questioned by a few participants, who felt that the trials population did not represent the type of problem drinking prevalent in the UK, and especially in Scotland, where drinking was said to be "*skewed towards higher risk levels and dependence*" (ID9, Psychiatry). Concern about the mismatch between the psychosocial support package used in the RCTs and the typical package that would be offered in UK primary care was also expressed, as this made the evidence less applicable to routine practice:

… there wasn't evidence that sort of standard support from the practice nurse or a GP would be enough because it was so different from BRENDA. So, it wasn't … it certainly wasn't really generalisable to general practice.
(ID12, Psychiatry)

Some dissenting views about the evidence were expressed by several participants from psychiatry who had worked with the drug company on nalmefene. One participant (who had also acknowledged weaknesses in the RCT evidence) felt that the cost effectiveness evidence submitted by Lundbeck was convincing, whilst another felt that the RCT evidence for nalmefene was strong – "*The most convincing arguments would be efficacy in randomised control trials*" (ID3, Psychiatry).

7.4.4.5 Comparative views of naltrexone for reducing alcohol consumption

Some participants expressed doubts about the extent to which nalmefene offered a new treatment. Almost half of participants talked of similarities between nalmefene and the existing drug naltrexone.[24] Nalmefene was described by one as an example of a "*me-too*" drug (ID16, Psychiatry), with other participants commenting that there was evidence to

[24] Like nalmefene, naltrexone is part of the opioid antagonist family of drugs but, unlike nalmefene, does not have a UK licence for the reduction of alcohol consumption. It can, however, be legally prescribed off-licence for this purpose.

suggest that naltrexone could also be used to reduce alcohol consumption. The pharmacological similarities between the drugs were mentioned:

> *Yes, you could use it in the same way, off licence, there is nothing stopping you. It's a very similar drug; it's quite difficult to determine where the differences are actually, in the formulation.* (ID19, Academic/Nursing)

One participant reported that naltrexone was provided as the first line treatment in his service because it was similar but cheaper than nalmefene:

> *I mean normally if a patient wanted nalmefene we would … and we were retaining them in the service then we would encourage them to have naltrexone instead of nalmefene because of its lower cost, but if they wouldn't buy that argument, if you like, we would give them nalmefene.* (ID12, Psychiatry)

However, others were cautious about prescribing naltrexone outside of its licensing conditions:

> *Naltrexone didn't have a licence for use in the UK. And for me, that was, you know, always a bit of a barrier, you know, when you're dealing with a relatively high risk group of patients, and for whom things can go wrong. And, you know, the idea of using a drug that wasn't fully licensed, with a patient group, was always one that I, you know, it meant you had to be cautious.* (P11, Psychiatry)

7.4.4.6 The nalmefene licensing conditions

Participants perceived the licensing conditions[25] as being challenging for primary care prescribers. This particularly related to the requirement for a diagnosis of alcohol dependence and the provision of psychosocial support. One felt that the requirement for patients to be both dependent on alcohol and drinking at high risk levels was "*confusing*" (ID1, Nursing) for clinicians, as high risk drinking did not readily map on to dependence. He added that this

[25] The licensing conditions for nalmefene require that patients: have a diagnosis of alcohol dependence but without withdrawal symptoms; are drinking at a high drinking risk level at initial assessment and two weeks later; and are given continuous psychosocial support alongside their medication.

was "*not what GPs would think an alcohol dependent person looks like*" (ID1, Nursing) and felt that nalmefene should have been offered based on drinking levels rather than an alcohol dependence diagnosis.

As discussed in Section 7.4.3 (prescribing experiences), concerns around whether patients with alcohol dependence were at risk of withdrawal symptoms were thought to make it challenging for clinicians to implement the nalmefene licensing conditions. Alcohol withdrawal was seen as often being linked with alcohol dependence, as pointed out by one participant:

> *I always thought it was a bit of a strange … to say alcohol dependent but not at risk of withdrawal because so much of alcohol dependence is defined by the risk of withdrawal …* (ID9, Psychiatry)

The licensing requirement that continuous psychosocial support be provided to nalmefene patients was viewed by some as being problematic for primary care. There was general agreement that the type of psychosocial support provided in the clinical trials could not be easily replicated in primary care and that input from specialist services was needed:

> *Those kind of longer interventions, brief interventions that are more than just simple advice are probably in reality not going to be done by busy frontline primary care roles rather than specialists and they don't really exist in primary care generally speaking*. (ID5, Alcohol Services/Commissioning)

7.4.4.7 The current alcohol treatment system

Most participants perceived that there were aspects of the current alcohol treatment system which made it difficult to prescribe nalmefene, either in primary care or specialist services. For GPs, prescribing nalmefene was felt to be challenging due to the perceived specialist skills required to properly diagnose, assess and monitor patients and the time constraints placed on them, as illustrated by one participant:

> *... unless you go for a specialist assessment and have the tools to do it properly and have them standing in front of the assessment tools, you are not going to be able to allow GPs to make a really clear decision against that diagnostic level of alcohol dependence. They could probably make a*

surmise as good as they can based on talking to the patient in eight minutes, but I think they are really going to struggle. (ID1, Nursing)

Prescribing nalmefene in primary care was also seen as challenging because it conflicts with the current treatment model in primary care – to offer brief advice to patients with alcohol problems and then refer them to specialist services. The reliance of primary care on specialist services to support people with more complex alcohol problems was viewed as a barrier for use of nalmefene. Moreover, it was felt by some that, as the typical patients seen in specialist services were generally not those for whom nalmefene is targeted, specialist services would be less able to offer advice to GPs:

Because I think if there was a conversation to be had, if a GP was asking me you know what's your advice, should we do this? I'd be saying well, not in our patient group; I have no experience of it and I guess that would get them to think, right well … should I or shouldn't I do this, and it would be difficult. (ID7, Psychiatry)

The involvement of specialist services clinicians in driving local formulary decisions on the use of new addiction medications was thought to make it more difficult to establish nalmefene as a routinely prescribed drug in some areas. Nalmefene was said to have been "*held up*" (ID12, Psychiatry) because of local drug and therapeutic committees' decisions not to approve it:

"So, if it was never approved, then it didn't go very far and often ... with addiction medications it's actually the specialist services who have to get them through the drug and alcohol … the therapeutic committees. (ID12, Psychiatry)

The "*budget culture*" (ID4, Psychiatry) resulting from changes in the funding and structure of specialist alcohol services was thought to reduce the likelihood that nalmefene would be prescribed by these services. Specialist services were said to be focussing their limited resources on "*core business*" (ID1, Nursing), such as methadone treatment and detox services. Some participants also commented that available services were "*less medically led*" than in the past (ID18, Academic/General Practice) as a result of their transfer out of NHS to local authority responsibility and also due to an increasing use of third sector and private

providers. These changes were said to make it more unlikely that a medical treatment like nalmefene would be considered:

> *The management by health and social services of alcohol problems has been moved out of the health sector into a possibly less expensive third sector arena where doctors and psychiatrically trained nurses ... familiar with the use of medication are not so widely employed.* (ID3, Psychiatry)

7.4.4.8 Beliefs and attitudes relating to alcohol problems and treatment

Clinicians' beliefs and opinions about alcohol problems and treatment were thought by some participants to have influenced the likelihood of prescribing nalmefene. According to one participant, Lundbeck had failed to realise this:

> *And I think what they hadn't realised is that when you get into the alcohol field it's much less to do with evidence than what people's personal opinion is about something and a firmly held belief. And I think, and as we know, it's really hard to challenge firmly held beliefs.* (ID14, Psychiatry)

Clinician beliefs acting as barriers to nalmefene prescribing were thought to include a "*pessimism*" (ID12, Psychiatry) about alcohol treatment based on a perception that good outcomes were rarely seen; a "*cynicism*" (ID5, Alcohol Services/Commissioning) about the benefits of pharmacotherapy for treating alcohol problems, especially in drinkers with mild dependence; concerns about over-medicalising this patient group; and a belief that abstinence-based approaches are the preferred treatment for alcohol problems:

> *I think even amongst a lot of primary care or non-specialist ... healthcare roles, the belief is if you've got an alcohol problem that means you're alcohol dependent and abstinence is your goal. That broader understanding of alcohol problems as a kind of continuum where cutting down fits in is lacking.* (ID5, Alcohol Services/Commissioning)

Public attitudes to alcohol were also viewed as barriers to nalmefene uptake, according to some participants. The normalisation by the general population of drinking high levels of alcohol, and the accompanying lack of acceptance or awareness of alcohol harms meant that patients who were potentially eligible for nalmefene were not asking for help with their alcohol problems. When patients did ask for help, it was said that their problems were often

too severe for them to benefit from nalmefene. A few participants also expressed a view that the medical profession did not regard alcohol use as seriously as other threats to health. One compared these with attitudes to tobacco:

> *The same isn't true for alcohol. There's a much less clearer picture, even though you we are now becoming more and more, I think, aware, that the threshold for alcohol's harmful effects is much lower. The profession as a whole, hasn't really bought into that. We still drink, I think as a profession, at the same, if not higher levels, as the general population. I think we have ambivalence about it.* (ID18, Academic/General Practice)

7.4.5 Nalmefene marketing activity: experiences, views and perceptions of its influence

Participants' accounts of Lundbeck's marketing and promotional activities covered the nature and scale of those activities, their opinions of those activities, and whether they perceived them to be successful in influencing nalmefene uptake in UK alcohol treatment.

7.4.5.1 Nature and scale of nalmefene promotional activity

Most participants were aware of nalmefene promotional work. They had experienced a broad range of activities including attendance at Lundbeck-sponsored events and contact by a drug representative. Some of the large-scale events were said to have involved high profile, well-respected speakers – "*you are not going to go much wrong with those two guys*" (ID8, Psychiatry). Smaller scale local meetings organised by Lundbeck were perceived to have various aims: to obtain expert opinion and advice on nalmefene; to inform the development of patient pathways and commissioning guidance for nalmefene; and to identify and educate key individuals, who could then raise awareness of the drug in their local areas – "*I think they were trying to see about creating little specialists who would advocate for nalmefene in the primary care setting*" (ID1, Nursing, talking about a meeting he attended to learn about nalmefene and how it worked). Some participants had been asked to work directly with Lundbeck on projects. These included alcohol-related projects initiated prior to the UK launch of nalmefene, which involved developing 'tools' for modelling the prevalence and impact of alcohol problems in local areas (discussed in Chapter 6, Section 6.4.2.3). Others had been asked to take on roles on nalmefene projects, including advisory roles, chairing meetings, or presenting at conferences.

The participants' accounts suggest that an extensive promotional campaign for nalmefene took place – "*it was heavily and quite aggressively marketed*" (ID16, Psychiatry). Lundbeck-organised events were widely publicised – "*I think they did a mass sweep of every addiction agency in the country*" (ID16, Psychiatry) and drug representative activity was described as "*very visible*" (ID17, Psychiatry). In some cases, the promotional work by drug representatives was said to have over-stepped local guidelines – "*if I remember correctly there was a mass email went out to … NHS staff directly, and I believe senior management had to pull someone in and say you can't do that.*" (ID6, Pharmacy). Some participants expressed surprise that Lundbeck representatives attended internal meetings:

> *… in my commissioning role, I was at a meeting in the hospital where we were trying to set up a more comprehensive alcohol team and he turned up at a meeting.* (ID5, Alcohol Services/Commissioning)

> *... I was surprised ... because normally, we'd ... been very clear about not working with or having clear boundaries between the alcohol industry ... but here was a pharmaceutical company, kind of, moving around those circles. I was quite uncomfortable about that.* (ID15, General Practices/Alcohol Policy, talking about a European alcohol meeting).

7.4.5.2 Views about the promotional activities and engaging with them

Many participants, regardless of their stance on nalmefene, viewed that some of the promotional work was beneficial in raising the profile of alcohol harms; raising awareness of the benefits of reduced drinking; and, generally, as valuable sources of information, education, training and networking, that were otherwise unavailable. Participants who had engaged with Lundbeck on nalmefene projects viewed these positively, describing a chance to learn about a new drug; to work with highly respected experts ("*luminaries*", ID14, Psychiatry) and clinicians from other countries; and to engage with GPs on delivering better care for people with alcohol problems:

> *… they were genuinely educational events, the people I met at these meetings included World Health Organization doctors and epidemiologists who I've since heard speak at other meetings and a couple of other consultants in addiction medicine, and I learnt an awful lot. And*

> *presumably a lot of other people who attended learnt a lot*. (ID2, General Practice)

However, some participants were critical about engaging with any of the Lundbeck-sponsored activities. Two had declined to work with Lundbeck on some of the early alcohol projects (discussed above), on the basis that these were 'marketing', as expressed by one participant:

> *It looked more like a market preparation research tool than a genuine alcohol impact model. And it felt more like they were trying to get me as an ally to start using their system in such a way that they would be improving the data within it. Which would help them to work out where their target markets would be when the medication came online, when it got licensed, which didn't happen for about three more years I think.*
> (ID13, Alcohol Services/Commissioning)

One participant felt it would have been "*ethically wrong*" (ID13, Alcohol Services/Commissioning) for him to accept the invitation to present at a Lundbeck-sponsored conferences – "*I just felt as though ethically you're receiving a benefit from the pharmaceutical organisations who are out to market medication for the sake of profit. So I thought it was out of order*." (ID13, Alcohol Services/Commissioning). By contrast, another participant, who had worked with Lundbeck on nalmefene projects, held a different view but acknowledged the potential for concern: "*I don't feel compromised, I am aware that there is a perception out there that working with industry can influence practice. I suppose that's a legitimate concern*" (ID19, Academic/Nursing).

7.4.5.3 Nalmefene marketing activities: perceptions of influence

Participants were asked to reflect on the impact of the promotional work. Some felt the promotional activities were initially successful and helped to establish nalmefene at national and, in some areas, local level. Positioning the drug as 'new' and 'novel' was said to increase its appeal and was thought to have engaged expert interest and support for nalmefene, whilst the efforts to engage local commissioners were thought to have facilitated development of pathways for prescribing alcohol dependence medications, including nalmefene. The promotional activities were said to have raised awareness of the drug and encouraged a short-term increase in prescribing in the UK (many participants commented that this was partly

helped by media reports on nalmefene). One participant felt that success in establishing nalmefene was less to do with the evidence for its efficacy, but rather to do with:

> *the way in which … the drug company seemed to be able to kind of play the system or kind of get it through the … get through the right kind of hoops and over the right hurdles to see it ultimately authorised by NICE* (ID5, Alcohol Services/Commissioning).

A few participants saw that there was a wider impact resulting from the promotional activities in shifting the discussion of the treatment of alcohol problems to one that was cognizant of the wider spectrum of alcohol problems, increasingly involved primary care, and increased awareness of the health benefits of reducing alcohol consumption:

> *… to change discussions around alcohol as being not merely just a, you know, you are either a drunk who needs to detox, or a person who is fine, and I think that that's I think in some ways it went someway to having those discussions and created these pathways.* (ID1, Nursing)

> *… it did bring to the fore in addiction specialists and particularly primary care … the advantages to health of reduction of drinking rather than what often was previously believed namely that abstinence was the only way to improve health outcome.* (ID3, Psychiatry)

Despite these initial successes, there was a general view that the marketing approach had not been successful in encouraging nalmefene uptake longer term:

> *... you know, so although SMC and NICE and formularies were persuaded to have it there, it still didn't take off.* (ID9, Psychiatry)

A number of reasons were offered. Firstly, and perceived by many as the most problematic for nalmefene, was the expectation that nalmefene would be prescribed in primary care. A few participants indicated the potential benefits of this in opening up the market for nalmefene to a potentially wide group of drinkers (one thought these would include harmful drinkers without dependence, which could be "*potentially a million or so people*" (ID5, Alcohol Services/Commissioning). However, the assumption that GPs would take the lead on nalmefene was considered problematic because it ran contrary to the current system for

managing alcohol problems. It was "*opening an new era*" (ID12, psychiatry) in which GPs would take the lead:

> *So that was my understanding of the approach that Lundbeck were taking, was to try to persuade general practitioners to, you know, be providing all of the management, including of course, the prescribing … which was the important bit for Lundbeck, without recourse to specialist services.* (ID11, Psychiatry)

The decision over the setting towards which nalmefene should be marketed was viewed as a dilemma by one participant from psychiatry, echoing the views of several other participants. Marketing to primary care was seen as being challenging due to this being "*a very disparate and widespread group*" (ID10, Psychiatry) who look to specialist services for guidance, whilst marketing to specialist services was problematic as they did not see the type of patients eligible for nalmefene, and could not therefore provide guidance to primary care:

> *You are not going to be able to influence the influencers because we are not the people who see this population. I understand the predicament.* (ID10, Psychiatry)

A second issue relating to the marketing approach, raised by a few participants from specialist services, was the strong focus on nalmefene as a medication for reducing drinking. One participant felt that more success may have been achieved for nalmefene if it had been marketed as a drug to help patients take a step towards achieving abstinence, as these were the types of patients they were seeing in services:

> *Because it was about reducing, but I think it may have been better if it was reducing to stopping, as a sort of a transition, a different way of, instead of sort of having five days of detox, then you're done and you go, this may happen over several months and you gradually reduce, and, ultimately, you're going to stop. So I think the thing about reduction but not necessarily abstinence sort of didn't help, and it wasn't something I particularly agreed with.* (ID14, Psychiatry)

Thirdly, some participants felt that more could have been done by Lundbeck to understand client groups, clinicians and ways in which nalmefene could fit into the current UK treatment

system. For some, this went beyond simply understanding what services do, but was also about understanding their "*culture, beliefs and wishes*" (ID18, Academic/General Practice):

> *But that's a really key thing, if you think you've got a product, and there's evidence that you've got a product that could add value, you've really got to understand how people are going to best use it, and why they would be motivated to use it. And I suspect that probably didn't happen adequately.* (ID18, Academic/General Practice)

7.5 Discussion

7.5.1 Summary and discussion of results

Many participants in this study welcomed nalmefene as an additional alcohol treatment option, especially as it targeted a group of drinkers whose needs did not appear to be well-served within the current system. Few participants had prescribed nalmefene, but their accounts provide additional insights and more nuanced understanding of nalmefene prescribing, complementing the information derived from the analysis of the GP data (Chapter 5).

Nalmefene was given to a broad range of patients with varying levels of alcohol problems and experience of treatment (some were said to be accessing treatment for the first time). Patient experiences were mixed, although little information about outcomes was collected. Of note is the suggestion that patients may not have continued with nalmefene beyond a single prescription because of the unpleasant side effects. In the Lundbeck RCTs, a high proportion of nalmefene patients experienced nausea (20 to 25%) and vomiting (6 to 18%) (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014a), and a recent meta-analysis reported that nalmefene patients were 3.2 times more likely than patients given the placebo to stop treatment due to side effects (Johansen et al., 2017). Among the other explanations offered for patients stopping nalmefene treatment include that it may only have had a small effect on their drinking. Low efficacy and side effects are thought to partly explain a large proportion of patient drop outs in a recent observational study on nalmefene (although the authors also suggest this could relate to inadequate support for these patients to help them adhere to treatment) (Barrio et al., 2019b).

A range of factors were thought to have influenced (positively or negatively) the uptake of nalmefene in the UK. The efficacy evidence was not thought to have encouraged uptake. If

anything, many participants' were doubtful about the efficacy claims and they cited issues associated with the nalmefene clinical trials, similar to those raised in the scientific literature (Spence, 2014; Palpacuer et al., 2015; Stevenson et al., 2015; Drug and Therapeutics Bulletin, 2016; Fitzgerald et al., 2016) and discussed in Chapter 3 (Section 3.4). These issues were thought to have dissuaded some prescribers from trying nalmefene with their patients. Interestingly, some had prescribed it to patients despite acknowledging its limited efficacy, suggesting that factors other than the evidence can influence prescribing. In this case it may imply that prescribers will try medications, even where the evidence is weak, in the hope that some individuals will benefit. Clinician views about treatment, knowledge of the patient and intuition are all factors that can influence their prescribing behaviour (Bruyninckx et al., 2009; Bonilauri Ferreira et al., 2010; Djulbegovic et al., 2018). The influence of clinician views about treatment was apparent in the nalmefene prescribing experiences, where participants expressed divergent views about the appropriateness of prescribing a medication for reduced drinking to patients with alcohol dependence.

Other factors may influence decisions to prescribe nalmefene, including the media. Participants recalled extensive media reporting of nalmefene. Although the level of media influence is uncertain, it was said to have encouraged some patients to ask their GP for nalmefene and had placed pressure on some areas to include it in local formularies. Media reports can influence the public, who can then act to influence prescribers (Prosser et al., 2003; Wathen and Dean, 2004; Edgar, 2013). The NICE TA recommending nalmefene as an option for treating individuals with alcohol dependence was also thought to have facilitated nalmefene prescribing in some areas. TAs place a legal obligation on NHS authorities in England to fund and resource the medicines they recommend, usually within a three-month period (NICE, 2018). Other studies suggest that NICE TAs can have a significant impact on primary care prescribing, although this is usually in combination with other factors (Wathen and Dean, 2004; Curtis et al., 2018).

A range of factors were perceived to have acted as barriers to nalmefene uptake. These include the availability of naltrexone, a similar, cheaper drug, for which there is evidence of efficacy in reducing alcohol consumption (Maisel et al., 2013; Donoghue et al., 2015; Castrén et al., 2019) but which is not licenced for reducing alcohol consumption. Many participants believed there to be little difference between nalmefene and naltrexone, leading some to view

naltrexone as the preferred option for reducing drinking; other participants were cautious about using a drug outside of its licensed indication.

Further perceived barriers to nalmefene uptake related to its licensing conditions. A particular issue for prescribers was the requirement that nalmefene be given to patients with alcohol dependence, who do not have withdrawal symptoms, a group that participants felt would be difficult for primary care practitioners to identify due to uncertainties around the risk of withdrawal. This was a specific issue for one of the specialist prescribers, who indicated he would only prescribe nalmefene to patients without dependence due to the risk of withdrawal, a concern raised by some other participants. The definitions of alcohol dependence adopted in the main disease classifications (DSM and ICD) (discussed in Chapter 1, Section 1.2.2) have broadened to recognise a continuum of problems, from mild to severe (American Psychiatric Association, 2013), and only sometimes involving a withdrawal state (WHO, 1992). Although these definitions recognise patients with mild dependence (the target group for nalmefene), it appears that this group are difficult to identify in routine clinical practice. The concerns raised in this study came from participants working in specialist alcohol treatment, whose experience may relate more to patients with severe dependence and a higher risk of alcohol withdrawal. Whether primary care prescribers would mirror this view is unclear. However, identifying alcohol dependence is challenging due to patients being unaware of, or under-reporting, their drinking problems (Goh and Morgan, 2017) and may be particularly challenging for primary care practitioners, given that concerns have been raised about their insufficient time, expertise and resources to address alcohol problems (Wilson et al., 2011; Derges et al., 2017; Holloway and Donoghy, 2017).

The licensing requirement that patients are provided with continuous psychosocial support was also perceived as a barrier for nalmefene. Participants commented that the required level of support could not easily be provided in primary care, concerns which had been raised in the ERG report on nalmefene (Stevenson et al., 2015). A series of different models of psychosocial support provision are likely to occur in clinical practice, as suggested by participants.

Systems-level barriers to nalmefene uptake related to the way alcohol problems were traditionally managed. The model of working described was one where primary care focus on providing brief advice on alcohol whilst specialist services manage patients with more severe levels of alcohol problem. In this system it is unclear who should have responsibility for

leading on nalmefene delivery. There was a view that nalmefene prescribing involved a level of skills, resources and time which would not be available in primary care, issues also raised in relation to delivering alcohol brief interventions in primary care (Wilson et al., 2011; Derges et al., 2017; Holloway and Donoghy, 2017). Financial pressures and structural changes experienced in specialist alcohol services were perceived as barriers to specialist service provision of nalmefene. Significant changes for alcohol specialist services were brought in with the Health and Social Care Act 2012 (*Health and Social Care Act*, 2012), including their transfer from the NHS to local authority responsibility and the opening up of the sector to competition from a wider range of independent and voluntary sector providers (House of Lords, 2016). Cost-saving measures as a result of this new Act have been highlighted, including employing lower-skilled workers in addiction services (Mohammadi, 2014; Krachler and Greer, 2015).

Certain attitudes were perceived to have had a negative impact on nalmefene uptake, including a pessimism about alcohol treatment, a scepticism about pharmacological treatments, a binary view of alcohol dependence and a general lack of engagement from primary care in addressing alcohol problems. Evidence from the scientific literature suggests high relapse rates among those entering treatment (Raistrick et al., 2006), only modest improvements among those given pharmacological treatments compared with placebo (Franck and Jayaram-Lindström, 2013; Drug and Alcohol Findings, 2015; Palpacuer et al., 2017), and abstinence still appearing to be the dominant treatment goal in specialist alcohol services (Witkiewitz and Marlatt, 2006; Klingemann, 2016; Goh and Morgan, 2017; Witkiewitz et al., 2017b; Rosenberg et al., 2020). Specific attitudinal barriers to implementing alcohol interventions in primary care include discomfort in asking about alcohol; reluctance to record alcohol information in medical records; fear of being perceived as judgemental, and concern about jeopardising the doctor-patient relationship (McAvoy et al., 2001; Tam et al., 2013). Patient lack of acceptance or under-reporting of problem drinking were thought to act as further barriers to nalmefene, resulting in patients not engaging with treatment until their problems were more severe, by which time nalmefene treatment may not have been appropriate. These problems have also been highlighted in primary care (Tam et al., 2013).

The widespread marketing described by interviewees, including the positioning of nalmefene as a novel treatment, were thought to have generated interest from alcohol experts, some of

whom in turn then supported further marketing activities. Expert opinion is held in high regard and can be influential in healthcare decision-making (Austin and Halvorson, 2019) and, as discussed in Chapter 2, the use of KOLs can add credibility to a message (Burton and Rowell, 2003). Participants noted that events were more likely to be attended if they were led by well-respected experts, creating a reinforcing loop whereby one aspect of marketing supports and/or reinforces another. Lundbeck's engagement with local commissioners was also thought to have facilitated the development of local pathways for alcohol treatment, which would include nalmefene (discussed in Chapter 6).

However, participant accounts suggest that, despite the extensive marketing and its initial successes in establishing nalmefene, the overall approach taken by Lundbeck was unsuccessful because of many of the barriers already described above. From a marketing perspective, it may have made sense to position the drug in primary care, as this would potentially offer the largest market for the drug and the best hope of engaging the group of drinkers for whom nalmefene is licensed. However, this assumed that GPs would be able to identify this specific group of drinkers, have the skills and confidence to prescribe nalmefene with little support from specialist services, and the resources available to provide the required psychosocial support (either in-house or via a specialist service). According to participants in this study, all these requirements for success were perceived to be lacking in primary care.

It was suggested that the marketing approach taken did not sufficiently consider the workings of the current alcohol treatment system. This included not only the roles and responsibilities of the different players in the system, but also differing attitudes and belief about alcohol problems and treatment, and why one approach might be favoured over another. Although a drug for reducing alcohol consumption was welcomed, the strong emphasis placed on its reduction properties alone meant that nalmefene would be viewed as less relevant to specialist services.

7.5.2 Strengths and limitations

These interviews were conducted to gain a deeper understanding of nalmefene use in the UK from the perspectives of stakeholders working in the alcohol field. They have generated rich contextual data on nalmefene which would have been difficult to obtain with other methods. The semi-structured interviews have enabled the collection of data to address the specific research questions but have also provided additional unanticipated insights on nalmefene

from participants' own experiences, for example, the role that attitudes and beliefs play in explaining low uptake of nalmefene.

7.5.2.1 Sampling

Purposive sampling, based on a range of sources, successfully identified expert participants, diverse in terms of their roles in alcohol treatment and geographic base. This diversity has been useful in generating insights on a drug that has been implemented differently in different areas, has been met with mixed opinions, and has been marketed to a wide range of stakeholders (as discussed in Chapter 6).

The extent to which qualitative findings can be generalised to a wider population or to different settings has been debated (Ritchie and Lewis, 2013). Whilst the sample recruited for this study cannot be considered representative of the views of those in the wider alcohol field, its diversity has allowed a variety of perspectives on nalmefene to be captured. The findings may thus offer 'representational generalisation' in uncovering the 'breadth and nature' of the topic being researched (Lewis et al., 2014, p. 351). A description of the sample characteristics has been included with the results so that readers can judge for themselves the extent to which some of the findings are relevant to their own role or setting, a concept referred to as 'reader generalisation' (Lewis et al., 2014, p. 352).

Appropriate qualitative sample sizes can be influenced by the heterogeneity of the population, the number of selection criteria, whether there are specific interest groups, the data collection method and available resources (Ritchie et al., 2014b). The target for this study (25 participants) was selected to meet the study's goals – a diversity of professionals from across the UK, a sufficient number of whom had experience of prescribing nalmefene, and/or had knowledge of how it was marketed. The total number of nineteen participants was short of the target, but considered to be sufficient to meet the main research objectives.

Only one of these nineteen participants was a GP prescriber, despite additional efforts to recruit GPs to the study. This reflects the challenges of recruiting GPs to research studies (Kaner et al., 1998; Salmon et al., 2007), but may also reflect how nalmefene has been used in clinical practice, in that many GPs have little experience of it (as indicted by the low prescribing in primary care). Most of the recruited participants were able to talk about nalmefene in the context of primary care, but additional insights from more GPs would have been beneficial in understanding the primary care perspective.

7.5.2.2 Data quality

A thorough description of the methods has been included to assist readers in assessing the quality of the findings. The topic guide and the themes used in the analytical matrix are available in Appendices 4 and 5. To enhance data accuracy, full transcripts of interviews were obtained, and checked by me. I also listened to the audio alongside these. Missing data or content where the meaning was unclear were also checked with individual participants (although only a few took up this offer).

7.5.2.3 Topic coverage

Not all participants could contribute consistently to all sections of the topic guide. For example, whilst some talked in detail about the licensing conditions or the clinical trials evidence, others had limited knowledge of these. Only half of the sample could talk about their prescribing experiences. These differences reflect the diversity in participants' backgrounds, experience and roles. In addition, participants were being asked to recall experiences and events which were not recent, and some had difficulties in remembering the details.

7.5.2.4 Practical considerations

Some participants could only offer a limited amount of time for interview, which restricted the time to follow up on issues raised. Aside from one interview, which was conducted face-to-face at the participant's request, all other interviews were conducted by telephone. This made it easier to interview participants from different areas of the UK, and provided some flexibility to re-schedule interviews at short notice, which is important to a busy group of professionals. However, data collected in telephone interviews have some limitations, including that neither the researcher nor the participant can observe any non-verbal interaction (Novick, 2008; Yeo et al., 2014). The telephone interviews in this study were sometimes problematic, as I had less control over the interview environment (one participant was walking along the street during part of the interview and there was considerable background noise in a number of interviews, making it difficult to decipher parts of the audio recording). However, most gaps arising from missing data were addressed either by the researcher listening to the audio files or via feedback from participants.

7.6 Conclusion

Treatment and policy stakeholders reported that the evidence for the efficacy of nalmefene in reducing alcohol consumption had a limited role in influencing nalmefene uptake in the current UK system, including encouraging or discouraging its use by clinicians. Rather, any appeal of the drug was felt to have come from its positioning as an intervention that could address a gap in current service provision, and potentially help many people not currently seen as well served by alcohol treatment options. This view of nalmefene is closely aligned with the messages established and promoted through a wide-ranging marketing strategy adopted by Lundbeck, as discussed earlier (Chapter 6), suggesting that the marketing was convincing and persuasive enough to win some support for the drug. Stakeholders reported that, despite such support, there remained substantial barriers to nalmefene being prescribed and used in the UK, including a lack of skills, resources and confidence in primary care to treat alcohol dependence, pressures on the wider alcohol treatment system, attitudinal barriers relating to views about alcohol problems and treatment, and its poor compatibility with the current system of treatment.

8 DISCUSSION

8.1 Introduction

This thesis employed a mixed-methods design to examine patterns in nalmefene prescribing in UK primary care, and to understand the factors influencing these. Four research questions (see Box 3) were addressed, using a combination of methods: a quantitative analysis of primary care prescribing data (Chapter 5); a qualitative documentary analysis (Chapter 6); and qualitative interviews with key professionals working in the alcohol field (Chapter 7). This discussion chapter aims to synthesise and interpret the key quantitative and qualitative findings from across these different elements of the thesis. The synthesised results are presented under themes which align broadly with the research questions, and are discussed in the context of the wider literature and implications for alcohol treatment and policy (Section 8.2). The contribution of the research is then outlined (Section 8.3) followed by implications for future research (Section 8.4). Next, the strengths and limitations of the research will be discussed (Section 8.5), followed by reflections on the research process (Section 8.6). The chapter ends with an overall thesis conclusion (Section 8.7).

Box 3: Research questions

1. To what extent and how has nalmefene been prescribed in UK primary care?
2. How has nalmefene been marketed and what influence has this had on the way in which the drug is perceived and used in the UK
3. What (other) factors have influenced nalmefene prescribing in UK primary care?
4. What are the perspectives of key stakeholders in the alcohol field regarding nalmefene, its promotion and its use in UK primary care?

8.2 Synthesis, interpretation and implications of the findings

Synthesised findings from across all three study strands are now presented and discussed in relation to the wider literature and their possible implications for alcohol treatment and policy. The evidence for nalmefene discussed in Chapter 3 in relation to its role in influencing nalmefene prescribing is referred to in the synthesised findings.

8.2.1 Understanding the extent and nature of nalmefene prescribing in UK primary care

8.2.1.1 Patterns in nalmefene prescribing

Analysis of national level monthly prescribing data showed that uptake of nalmefene in UK primary care was low, which is consistent with qualitative participants' experiences and with primary care's prescribing of other alcohol dependence drugs (Thompson et al., 2017). Reasons for low uptake of pharmacological interventions for alcohol problems include modest effects, lack of skills and knowledge relating to medications and financial factors (Thomas et al., 2003; Thompson et al., 2017; Williams et al., 2018). Whilst some of these likely also apply to low use of nalmefene, other explanations specific to nalmefene and its licensing conditions are also suggested by this study and may partly explain its relatively lower use compared with other alcohol dependence medications (NHS Digital, 2018).

Most nalmefene patients received only one prescription of the drug, in line with other alcohol dependence drugs prescribed in primary care (Thompson et al., 2017). The qualitative findings, along with evidence from the clinical trials, suggest that a combination of factors contributed to lack of repeat prescriptions, including unpleasant side effects, that nalmefene had little or no effect in reducing alcohol consumption, and that one prescription of tablets may have been sufficient to help some patients (because tablets can be taken 'as-needed', rather than daily). On balance, it may be that side effects were particularly problematic for nalmefene patients, as evidenced by the high proportion of patients prescribed with nalmefene who had experienced unpleasant side effects in the RCTs (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014a) and a meta-analysis of nalmefene RCTs in which patients were 3.2 times more likely than placebo patients to stop taking the drug due to the side effects[26] (Johansen et al., 2017). A lack of support for patients to engage with their medication may also partly explain why so few continue beyond one prescription (Thompson et al., 2017); few patients prescribed with nalmefene had data in their GP record indicating receipt of psychosocial support.

[26] Proprtionally, 12.8% of patients prescribed with nalmefene and 3.5% of patients prescribed with the placebo withdrew due to adverse events in this study.

Qualitative accounts add some weight to the interpretation deriving from the prescribing data that nalmefene may have encouraged new patients into treatment. Half of the patients who had been prescribed with nalmefene had no formal alcohol treatment recorded in their GP record prior to receiving nalmefene, and participants in the qualitative study talked of new patients coming forward, suggesting that nalmefene may have "*opened up the service to people who might not have accessed it before*" (ID17, Psychiatry). Given this participant's background (specialist services), the quotation implies that nalmefene encouraged a new type of patient into specialist alcohol treatment, rather than primary care. However, the route to treatment may have been via primary care (as a result of patients reading media articles on nalmefene).

Analysis of patient-level data suggested many patients did not align with the conditions specific to the licensing of nalmefene (i.e., they did not have an alcohol dependence diagnosis, were not drinking at a high DRL, had not received a pre-nalmefene assessment, or had not received adjunct psychosocial support). Notwithstanding likely anomalies in the data recorded on the GP system (as discussed in Chapter 5, Section 5.5.3), the qualitative accounts largely supported this: nalmefene was prescribed to patients with differing levels of alcohol problems and to individuals outside of the licensed group, including binge drinkers and those without alcohol dependence. Participants' accounts, alongside evidence from the wider literature, provide insights into why real-world prescribing of nalmefene differed from its licensing conditions.

Despite alcohol dependence being a requirement of the licensing, less than half of nalmefene patients had this diagnosis recorded in their GP record. Although under-recording of alcohol data (discussed in Chapter 5, Section 5.5.3) may partly explain this, the qualitative findings suggest there may be a reluctance to prescribe nalmefene for alcohol dependence due to the risk of withdrawal associated with dependence (licensing for nalmefene states it should not be prescribed to patients with withdrawal symptoms). This may suggest that attitudes to alcohol dependence may be aligned more with traditional binary model definitions rather than continuum approaches which recognise that dependence can also present at mild and moderate levels (as discussed in Chapter 1, Section 1.2.2) (Hasin et al., 2013; Stockwell, 2015). It is worth noting that these attitudes came from participants working in specialist services (rather than primary care), whose experience will have derived mainly from seeing patients with more severe dependence, for whom reduced drinking approaches such as

nalmefene may be less relevant. An unawareness or downplaying of alcohol problems makes it challenging for clinicians to diagnose alcohol dependence in individuals (Goh and Morgan, 2017). The findings on nalmefene raise questions about how alcohol problems are diagnosed by clinicians, and what beliefs and definitions about dependence underpin these. Binary models of dependence may be unhelpful in recognising and addressing the needs of the significant group of harmful drinkers (who may or may not have some level of dependence).

Quantitative and qualitative findings from this study suggest difficulties for primary care in providing psychosocial support to nalmefene patients, which is consistent with research on the prescribing of other alcohol dependence drugs in UK primary care (Thompson et al., 2017). Regular psychosocial support, recommended alongside all pharmacological treatment for alcohol dependence (NICE, 2011), was also part of the nalmefene licensing conditions and, crucially, was one of the conditions under which nalmefene was shown to have a potential (sub-group) effect in the RCTs. Prescribing data suggest few patients who had been prescribed nalmefene received this support in primary care, and the qualitative findings point to limited provision within specialist alcohol services due to resource constraints. There is a need for this support to be adequately funded, both for patients using alcohol dependence medications and more widely.

8.2.1.2 Implications of real-life prescribing patterns for evidence-based medicine

These findings suggest that the nalmefene trial evidence does not easily translate into clinical practice, and this has implications for evidence-based practice. The risk is that nalmefene is prescribed to patients for whom there is either no RCT evidence of benefit or RCT evidence of no benefit. For example, this may happen where nalmefene is given to patients without first reassessing their drinking level two weeks after initial assessment. This two-week waiting period was a key basis on which the drug was licensed because, in the trials, nalmefene was only found to be effective (via a post-hoc subgroup analysis) in those who had not already cut down their drinking after this two-week period. If this two-week waiting period is not implemented in normal practice (as suggested by the prescribing), there is a risk that nalmefene is given to patients who may not have needed it, as they may have been able to reduce their drinking by themselves.

Whether the RCT evidence, which derived mainly from specialist care settings, was relevant to primary care practice, was an issue, as for RCTs in general (Jacobson, 1997). Trials with a pragmatic design including less stringent eligibility criteria and a spectrum of participants

most likely to be offered treatment under 'usual conditions' may be more applicable (Rothwell, 2006; Loudon et al., 2015; Pawson, 2019). For nalmefene, a pragmatic design may have provided an opportunity to evaluate efficacy in a wider group of patients and settings, reflecting some of the real-world uncertainty around diagnosing alcohol dependence and the heterogeneity of alcohol problems among patients accessing primary care.

The nalmefene experience raises questions for licensing policy. Is it appropriate to apply stringent licensing conditions to medications when those conditions are not applicable in routine practice? Although the appropriate setting for nalmefene was debated at the time, any recommendation on setting was deemed outwith the remit of NICE TAs (Stevenson et al., 2015). The applicability of RCT evidence is not generally considered by NICE (Brown and Calnan, 2013), but the implementation problems identified in this study suggest that this remit should be widened.

8.2.2 The role of marketing in influencing uptake of nalmefene in the UK

8.2.2.1 Marketing activity and its potential influence

The marketing of nalmefene in the UK was both wide-ranging and intensive (Chapters 6 and 7). With Lundbeck support, nalmefene was promoted in the scientific literature, with claims about efficacy which downplayed some of the limitations of the evidence (discussed in Chapter 3, Section 3.4). These papers have likely influenced the wider scientific literature, including narrative reviews and systematic reviews and meta-analyses (Ross et al., 2012). The framing of nalmefene as a 'novel' approach with potential to engage new patients into treatment (Chapter 6) may have been persuasive in generating support for the drug. Ideas and framing messages can be as influential as evidence (Smith, 2013), and these are used by pharmaceutical companies in planning publications around particular themes thought to facilitate uptake of their products (Ross et al., 2012). The extent to which this supportive scientific literature influenced prescribers is unclear, although participants in this study (mainly specialists) knew of the RCT limitations and held doubts about the evidence (even those who had prescribed nalmefene). Generalist prescribers, who may be less able to access and critically appraise scientific literature (Prosser et al., 2003), may not have had this knowledge about the limitations of nalmefene. Whilst the supportive literature on nalmefene may not have had a direct impact on prescribers, it was influential in other ways – it fed into some of the Lundbeck-supported activities around alcohol, including the ICP work and conferences and educational events, as discussed in Chapter 6.

Stakeholder marketing activities identified in the documentary analysis brought Lundbeck into contact with a wide range of organisations and individuals. These activities had potential benefits in influencing uptake of nalmefene. The stakeholders identified have influence in various ways – they contribute to media reports, are consulted in assessments of new medications, and contribute to policy debates and decisions about treatment provision. Importantly, they offer a channel through which pharmaceutical companies can relay positive messages relating to their products (Buttle and Boldrini, 2001; Rothman et al., 2011; Edgar, 2013). The perceptions of participants in the qualitative interviews suggest that these activities were beneficial for nalmefene: the influence of KOLs used by Lundbeck was helpful in promoting nalmefene; joint projects with alcohol service commissioners were helpful in establishing it in some local care pathways; and the media reporting may have helped encourage some new patients to come forward for nalmefene (Chapter 7).

8.2.2.2 Risk of bias arising from marketing

Bias relating to these funded activities can occur in a number of ways. By supporting the scientific literature, Lundbeck may have helped present an overly optimistic picture of nalmefene efficacy, whilst downplaying the limitations of the RCT results. Whilst peer review processes and guidelines for conducting, reporting and publishing clinical evidence exist (Moher et al., 2010; ICMJE, 2019), there are still problems with reporting quality (Dwan et al., 2011; Goldacre, 2013; Goldacre et al., 2019), including reporting in clinical trials in the alcohol field (Witkiewitz et al., 2015a). Maintaining independence in the publishing system is important, but is complicated by the financial relationship between journals and the pharmaceutical industry, who pay for advertisements, supplements and special editions (Goldacre, 2013).

Stakeholder marketing activities may work at a wider level to introduce bias into health care decision-making, even if transparently declared. Supported activities in which there was 'partnership' working (for example the ICP projects) may have presented Lundbeck with an opportunity for more direct influence, in this case, in shaping local care pathways. The risk here is that these pathways were influenced by commercial interests, possibly at the expense of other evidence based interventions and scarce NHS resources. Although some funded activities (support for charity reports) appear to offer little opportunity for direct influence, they may introduce bias in more subtle ways. Those in receipt of funding may be unaware of potential bias resulting as bias can be unconscious (Dana and Lowestein 2003). Even small

amounts of pharmaceutical funding may generate a reciprocal response from the recipient (Association of American Medical Colleges and Baylor College of Medicine, 2007) and can act to influence (consciously or subconsciously) their activities or their standpoint on a product (Mintzes, 2007; Fabbri et al., 2020). There are therefore unavoidable risks of bias when organisations in receipt of funding from a particular pharmaceutical company, then contribute to advisory body assessments of that company's product (as with the NICE TA assessment of nalmefene) or help shape other national advisory documents (Section 6.5.3.2).

8.2.2.3 The importance of transparency

At the very least it is necessary to ensure that links to pharmaceutical companies are clearly disclosed. Links to the drug company were not always clear in the scientific papers examined in this study. Although journal policies relating to COIs have been strengthened (ICMJE, 2019), gaps remain which make it difficult for readers to assess for bias (Grundy et al., 2020). Suggested solutions include asking authors to disclose all relationships and activities they have had with pharmaceutical companies, placing the onus on readers to judge whether this presents bias (Taichman et al., 2020) and the establishment of a publically accessible database of detailed information on author COIs (Grundy et al., 2020). Whilst this information is likely to help improve transparency, assuming it is accessible for readers, it does not address the issue of potential bias (discussed in Section 8.2.2.2).

Whilst Lundbeck funding was disclosed for many of the funded activities (for example, funded reports or conferences), the links to the company were not always transparent in further activities undertaken by funded organisations or individuals (for example, in contributions to NICE guidance to support the implementation of nalmefene and in media articles about nalmefene) (Smith, 2012; Ross, 2013; NICE, 2015). Some disclosure policies are being reviewed, including the NICE policy for organisations contributing statements to their advisory committees (Leng, 2019), and pharmaceutical companies are now asked to disclose information about payments to health care organisations and professionals via the Disclosure UK database. The latter is industry self-regulated, however, and contains gaps in the information disclosed (Mulinari and Ozieranski, 2018). Many NHS organisations in the UK have failed to disclose pharmaceutical industry funding (Moberly, 2018, 2019), although revised guidance has been published which includes more detailed requirements on managing COIs, including keeping registers of interest up to date (NHS England, 2017).

8.2.2.4 Beyond transparency

Transparency in declaring a COI is the main policy approach to mitigate any negative effects relating to COIs (Loewenstein et al., 2011). However, improving transparency will not eliminate the risk of bias from pharmaceutical funding of health care activities. Research suggests that disclosure of interests may have 'unintended consequences', including weakening concern among readers about potential bias because disclosure implies some honesty (Cain et al., 2005; Pearson et al., 2006; Loewenstein et al., 2011). Other readers may simply not know how to deal with the disclosed interests, and may just ignore them (Loewenstein et al., 2011). As mentioned above, individuals who declare a potential COI, may not be conscious of any resulting influence on their work or practice.

Greater transparency will also not address the potential shift in agendas across whole sectors, including research, medical education, charities, patient groups and the wider health service, resulting from pharmaceutical industry supported activities (Edgar, 2013; Goldacre, 2013). Initiatives supported with funding will have more opportunities to influence debates on health policy (Edgar, 2013) and potentially deflect funding towards commercial interests (Moberly, 2019). In relation to alcohol policies, those policies without commercial backing, including well-evidenced population measures for reducing alcohol harm as well as psychosocial approaches to treatment (discussed in Chapter 1, Section 1.3), may be given less prominence.

To reduce risk of bias, policies should aim to reduce the number of individuals (clinicians, academics and those involved in the regulatory system) and public and charitable sector organsiations funded by pharmaceutical companies. Approaches to increase independence in health research, education and clinical practice are required, including publically-funded trials, independent evaluations of trials, reforms to the way patient organisations are funded and conflicts of interest managed, tighter restrictions on marketing to health care professionals, and the removal of industry involvement in both the regulatory system and medical education (Moynihan et al., 2019; Rickard et al., 2019). Had some of these policies been in place, it is possible that nalmefene uptake could have been even lower than reported. For example, if Lundbeck had not funded various stakeholders, there may have been fewer organisations or individuals submitting supportive statements to the NICE assessment, fewer ICPs favourable to nalmefene, and less support for the drug generally due to reduced exposure to the marketing messages.

It may be challenging to implement such policies. Currently, public and third sector organisations (including charities supported by Lundbeck) are facing large cuts in government funding, creating pressure to accept funding from private companies in order to continue their work (Baggott and Jones, 2015). This culture of reliance on, and acceptance of, pharmaceutical involvement may be difficult to change. Industry-healthcare collaborations are encouraged by government and the NHS, including joint working with CCGs to develop care pathways (Department of Health, 2008; Praities, 2012). A more independent healthcare sector would require more public funding for organisations involved in health care and health care advocacy, and for research, including clinical trials. It is notable that, during the COVID-19 epidemic, it was a new financial model of large amounts of government funding, channelled to and through the pharmaceutical industry and academia, that enabled the rapid progress in vaccines research and development (albeit any profits generated going to the pharmaceutical companies) (Bloom et al., 2021; Sampat and Shadlen, 2021). Interestingly, some companies (Astra Zeneca and Johnson & Johnson) agreed to make the vaccine available on a non-profit basis, at least initially (Dyer, 2021).

8.2.3 The role of other factors in influencing nalmefene prescribing in UK primary care

Apart from marketing activity, there were other factors related to the uptake of nalmefene in the UK. The positive NICE recommendation on nalmefene (in the form of a TA) appears to have been influential in increasing primary care prescribing, as demonstrated by the time series analysis (Chapter 5, Section 5.3) and as has been found for other drugs (Wathen and Dean, 2004; Curtis et al., 2018). Findings from the qualitative interviews (Chapter 7) and documentary analysis (Chapter 6) demonstrated the role and importance of the TA in influencing nalmefene uptake. Several supportive statements were submitted during the TA process from well-respected national charities or patient groups with links to Lundbeck (Section 6.5.3.1). These may have influenced NICE decisions (Dakin et al., 2006), including facilitating acceptance of nalmefene. In turn, Lundbeck-supported publications recommended adherence to NICE prescribing guidelines (Chapter 6). In qualitative interviews (Chapter 7), participants saw the TA as beneficial in influencing uptake and recalled that it was mentioned by Lundbeck drug representatives in promoting nalmefene.

In combination with the NICE TA and accompanying press release, media reporting on nalmefene appears to have influenced patients to ask their GP about nalmefene (Chapter 7).

This illustrates the power of media in influencing patients, consistent with other research (van Bekkum and Hilton, 2013; Henderson and Hilton, 2018). Whilst they may raise public awareness of new medicines or treatment, media reports can be misleading due to inaccuracies in the information presented, and they tend not to disclose any COIs for individuals or organisations who have contributed supportive statements relating to the product (Cook et al., 2007; Doherty and Carroll, 2021).

Other factors may influence decisions on whether to prescribe a drug, including a clinician's own views about treatment, what they know about the patient, and their intuition (Bruyninckx et al., 2009; Bonilauri Ferreira et al., 2010; Djulbegovic and Elqayam, 2017). Interviewee reports suggested that some individual prescribers tried nalmefene with their patients, apparently in the hope that it would work for some individuals, despite regarding the evidence as weak, and that this was prompted at least in part by a lack of effective treatment options for some patients (Chapter 7). A lack of treatment options and high rates of relapse post-treatment for alcohol problems have been highlighted (Raistrick et al., 2006) and may influence GP decisions to prescribe new medications (Prosser et al., 2003)

8.2.4 Considering the importance of system-level influences

Taken together, all of these factors – the marketing activities, the NICE TA, the media reporting and an under-resourced treatment system – may have helped generate support for establishing nalmefene as a treatment for alcohol dependence and encouraged some prescribers to try it with their patients. However, the case of nalmefene provides an example of where pharmaceutical marketing has ultimately failed, as evidenced by the low uptake of the drug. There were other stronger influences which prevented it from being used as widely as sought by Lundbeck.

Firstly, the model that Lundbeck advocated, with nalmefene mainly prescribed in primary care with little support from specialist services, conflicted with current practice. GPs provide brief interventions/advice on alcohol, but mainly refer patients with dependence to a specialist alcohol service. Participants in the qualitative interviews expressed concern that GPs would have insufficient time, skills or resources to identify patients and prescribe nalmefene in accordance with its licensing conditions. Similar issues have hindered the delivery of less complex alcohol interventions in primary care (Wilson et al., 2011; Derges et al., 2017; Holloway and Donoghy, 2017). A recent systematic review on barriers to delivering screening and brief interventions in primary care identified time constraints on

GPs and a perception that screening and brief interventions were too time consuming. This same review identified that GPs had difficulties in distinguishing between harmful drinking and alcohol dependence and in knowing how to identify people drinking at risky levels who are not showing symptoms of alcohol problems (Rosário et al., 2021). Both issues are relevant in identifying patients eligible for nalmefene.

Secondly, whilst prescribing nalmefene in primary care was problematic, neither did it fit in with specialist alcohol services provision (Chapter 7), where the focus is on treating patients with more severe alcohol dependence, and where abstinence is the most common treatment goal. As a drug for reducing drinking, nalmefene may have been seen as being of limited value in these services. This is consistent with studies suggesting that abstinence remains the dominant treatment goal in specialist alcohol services (Witkiewitz and Marlatt, 2006; Klingemann, 2016; Goh and Morgan, 2017; Witkiewitz et al., 2017b; Rosenberg et al., 2020). Broader challenges, such as a de-prioritisation of alcohol problems in addiction services and a lack of medical prescribers in community services (Clark and Simpson, 2014; Alcohol Research UK, 2018), may also have worked against nalmefene.

Thirdly, the nalmefene treatment model involved a new patient group, whose pathway in the current treatment system was not well-established, leaving uncertainty over who has responsibility for this group of drinkers. Lundbeck were positioning nalmefene as a potential solution to addressing the needs of this patient group, but required a dramatic system-level change for this to work – they called for "*a radical redesign of alcohol treatment services*" (Lundbeck Ltd., 2014e, p. 4). Their hope was for a system where GPs take a greater responsibility for treatment of mild alcohol dependence, and can provide psychosocial support to patients with little need from a specialist alcohol service, both of these being difficult to achieve for reasons already discussed.

Fourthly, an attitudinal change was required to implement nalmefene treatment (Chapter 7). Barriers within the treatment system (primary care and specialist services) included pessimism about alcohol treatment and pharmacological approaches, a binary view that alcohol dependence is distinct from other alcohol use disorders, and a lack of engagement in primary care. These have all been cited as barriers to implementing other alcohol interventions in primary care (McAvoy et al., 2001; Tam et al., 2013). Public attitudes were also cited as barriers to use of nalmefene, as the target population was a group of drinkers

who underplay their drinking, may not consider themselves to be problem drinkers and often do not recognise the consequences of their drinking (Garnett et al., 2015; Parke et al., 2018).

Lundbeck may have been attempting to mitigate some of these system-level barriers via their support for certain alcohol-related activities, for example, activities advocating greater investment in alcohol treatment, a greater role for primary care and a change in attitudes (as discussed in Chapter 6). However, these activities may not have been sufficiently nuanced towards the specific conditions needed within primary care to enable GPs to take a lead role in identifying and treating the nalmefene patient group, including what might motivate GPs to do this. Another system-level barrier for nalmefene may also relate to the fact that the GP General Medical Services contract does not explicitly require GPs to provide alcohol treatment to patients (NHS England, 2020; Scottish Government, 2017). It was difficult to recruit GPs into this study, and engaging them in the promotional work for namefene may also have been challenging for Lundbeck. Most of the 'champions' recruited by Lundbeck to act as KOLs were from the specialist addiction field rather than primary care.

8.2.5 Considering the role of primary care in addressing alcohol problems

The nalmefene experience, in line with other studies, highlights the challenges of implementing alcohol interventions in primary care, and raises questions about the primary care role in addressing alcohol problems. However, there are compelling arguments for primary care to take a lead role. Because GPs see a large percentage of the population, they have an opportunity to identify patients across the whole continuum of alcohol problems (Rehm et al., 2015). Being able to access alcohol treatment via primary care rather than specialist alcohol services may also encourage more patients to come forward, as it helps avoid the stigma associated with getting alcohol treatment (Andréasson et al., 2013). Finally, there is evidence that supports primary care delivery of interventions for alcohol problems, including some interventions (brief psychosocial support among these) for patients with alcohol dependence (Andréasson et al., 2013; McCambridge and Rollnick, 2014).

New models of alcohol treatment in primary care should consider the skills and resources required by GPs to identify alcohol problems, agree treatment goals and provide appropriate options for treatment, including pharmacological treatment. The findings from this thesis support research-based recommendations to support GPs to provide alcohol treatment, including the following:

- specific alcohol training and resources for primary care staff, including how to identify different levels of alcohol problems, training on pharmacological options, and how to motivate staff;

- involving a range of staff throughout the practice in identifying and supporting at-risk drinkers;

- increasing understanding of how discussions about alcohol actually happen in primary care and what helps to engage patients; and

- the identification of ways to promote to the public the GP role in addressing alcohol problems (Andréasson et al., 2013; McCambridge and Rollnick, 2014; Williams et al., 2018; Rosário et al., 2021).

New ways to encourage behavioural change in harmful drinkers are also needed, including the promotion of continuum beliefs about alcohol problems, which are reported to help individuals recognise their alcohol problems (Morris et al., 2020).

A strategic discussion to clarify the role of primary care more generally in managing alcohol problems is needed (McCambridge and Stewart, 2020), including its role in preventing alcohol-related harms as well as treating alcohol problems (McCambridge and Saitz, 2017). The need to address alcohol problems at an early stage is great, with alcohol-specific deaths in some parts of the UK reaching their highest level yet (Office for National Statistics, 2021) and with concerns about increased drinking in the population during the lockdowns associated with the COVID-19 pandemic (Clay and Parker, 2020; Kim et al., 2020). Ways in which primary care can be involved in this should be researched and evaluated, including how to encourage the public to engage with primary care and how primary care staff can initiate discussions about alcohol, as outlined above. Both require a change in behaviour (among clinicians and patients) and it is encouraging that recent research has utilised behaviour change theories in understanding barriers to implementing alcohol interventions in primary care (Rosário et al., 2021; Wallhed Finn et al., 2021).

8.3 Novel contribution to knowledge

This research broadens knowledge about nalmefene and the wider alcohol treatment context in the UK. To my knowledge, it is the first study to use time series analysis to demonstrate a

strong, but short-lived impact of NICE guidelines in encouraging nalmefene prescribing, and the first to shed light on how nalmefene has been used in primary care practice, including the extent to which its licensing conditions were adhered to, by examining patient-level prescribing data from UK primary care. Whilst other clinical studies subsequent to the RCTs have evaluated nalmefene use in clinical settings, these have been limited to studying use in the licensed patient group (Castera et al., 2019) or small numbers of patients from outside of the UK (Di Nicola et al., 2017; Barrio et al., 2018; Barrio et al., 2019a; Barrio et al., 2019b). It is also the first study to systematically describe a range of nalmefene marketing activities using scientific and grey literature to provide an in-depth account, giving novel insight into the activities, the stakeholders involved, and their potential influences. Finally, no previous study has conducted interviews with professionals working in the alcohol field to add to understanding of nalmefene's place and use in the UK.

8.4 Implications for future research

This study highlighted the gap between prescribing recommended in guidelines and real-world prescribing practice. Future research on new pharmacological approaches to alcohol interventions aimed at primary care should be evaluated, taking account of the primary care prescribing context.

The potential distortion of RCT evidence from the activities of pharmaceutical companies, and the impact of stakeholder marketing activities on prescribing and health care decision-making is concerning. Alternative models of working to facilitate greater independence from the pharmaceutical industry, including funding models for RCTs, could be explored.

This study has highlighted the limited available options to address the needs of harmful drinkers, or those with mild dependence, to reduce their drinking. Further research could focus on strengthening the evidence base by evaluating the effectiveness of interventions specifically targeted at this group of drinkers (whether psychosocial, pharmacological or a combination of these). Given the significant numbers of patients enrolled in nalmefene RCTs who managed to reduce their drinking without medication and with little intervention, further research to identify ways to support these individuals to reduce their drinking by themselves may be helpful. The difficulties in distinguishing between different types of drinker have also been highlighted (Rosário et al., 2021) and it would be valuable to research effective

strategies for identifying harmful drinkers and those with mild dependence (both through self-identification and identification via primary care).

If primary care is to have a greater role in addressing alcohol problems, including in harmful drinkers or those with mild dependence, there needs to be further research to identify efficacious models of delivery of alcohol interventions in primary care, and how those might effectively be introduced into routine practice. Considerable research is available on barriers to implementing alcohol interventions in primary care, but further research might focus on how to increase the demand for alcohol interventions and what might help encourage individuals drinking at risky levels to engage with primary care. This could explore strategies for raising public awareness that they can talk to their GP about their alcohol problem, an issue raised in relation to primary care treatment of alcohol problems (Andréasson et al., 2013; McCambridge and Rollnick, 2014). Primary care could play a role in helping to prevent harmful drinking in the first place (McCambridge and Saitz, 2017), and more research could help identify ways in which they can be supported to do this.

Further research to address some of the gaps identified in this study may also be beneficial, including research on GP perspectives of prescribing nalmefene and research on media framing of nalmefene and its potential influence. Qualitative work with patients (perhaps through online patient forums) who have received nalmefene would help provide a more nuanced understanding of pathways to receiving nalmefene, what has influenced these, and experiences of taking nalmefene.

8.5 Strengths and limitations of the research

The strengths and limitations relating to the approach used in each study within the PhD have been discussed in detail in respective chapters (Chapters 5, 6 and 7). This section discusses the strengths and limitations of the overall approach taken.

8.5.1 Strengths of the research

A key strength of this study is the mixed-methods research design itself, which was appropriate for addressing the main study aim. Data from the three study strands have been integrated to provide a more comprehensive understanding of nalmefene prescribing and factors that have influenced this in the UK. Triangulation of the findings across the strands gives greater confidence in key findings, including: the mismatch between real-world nalmefene prescribing and that proposed by the nalmefene licensing conditions; key

influences on nalmefene prescribing, including the role of the nalmefene TA; and the extent and influence of nalmefene marketing. In particular, the concurrence between findings derived from the prescribing data and those from the qualitative data adds confidence to some prescribing data findings that are uncertain due to known data recording issues.

Each element of the study had its own strengths, as discussed in each chapter. Firstly, the systematic literature search informing the discussion of the nalmefene evidence base in Chapter 3 was conducted according to PRISMA guidelines. Secondly, the prescribing analysis derived from two robust and highly-validated prescribing datasets. Thirdly, the documentation used to examine nalmefene marketing was based on an extensive search of both the scientific and grey literature. Fourthly, interviews were conducted with a wide range of alcohol experts, providing a diverse range of views and experiences of nalmefene.

8.5.2 Limitations

This study is subject to a number of limitations. Firstly, it is impossible to consider all available data on any topic, and the scope of the study was limited by available time within the PhD.

Individually, each study strand had its own set of unique limitations which are discussed in detail (Chapters 5, 6 and 7). An important aspect of validity in mixed-methods designs is to consider whether parts of the data collection, analysis and interpretations deriving from the individual study strands might compromise the integration of data and any conclusions made (Creswell and Plano Clark, 2011). In this study, data about nalmefene were collected from three quite distinct sources (documentary materials, GP records, and interviews with a range of professionals). Whilst the connected data have enabled a more complete and robust understanding of nalmefene prescribing, there are some limitations associated with the merging of these differing data types. For example, despite efforts to recruit GPs into the qualitative sample, interviews were conducted with participants mainly from an alcohol specialist services background (only one participant was a current GP prescriber). This has placed limitations on the extent to which data from the qualitative interviews can explain or add insights on primary care prescribing patterns. Under-reporting of alcohol data in GP records has introduced uncertainty into some of the findings (for example, the proportion of nalmefene patients meeting the high DRL requirement of the licensing conditions), and it was not always possible to corroborate these using qualitative interviews (particularly as GPs were under-represented in these).

Interviews with a broader group of GPs, patients, and individuals from a range of other organisations (including Lundbeck, funded organisations, and the regulatory bodies) were not obtained, which means that other possible perspectives on the value of nalmefene, and its marketing and use in UK primary care, have not been obtained.

As also discussed in Section 4.5, the approach taken and the conclusions reached may be subject to researcher bias. The outline of the PhD was written by one of my supervisors, who also led on a paper questioning the evidence for nalmefene (Fitzgerald et al., 2016). This will have influenced my perspective on nalmefene to some extent; however, it is rarely possible to be completely objective as a researcher (Bryman, 2012). I have recognised this potential bias throughout my PhD, and sought to remain reflective and to critically question and discuss my supervisor's and my own developing views as the work progressed. I have also searched for and read extensive sources, both critical and supportive, and have deliberately sought out interviewees with a balance of views about nalmefene.

8.6 Reflections on the research

This PhD journey has been rewarding and challenging. My background as a social researcher was mainly in largescale survey research, and the PhD has helped widen my skills to include qualitative and mixed-methods research and to gain in-depth research expertise in an interesting and important policy area. I have greatly enjoyed meeting other researchers within and outside of ISMH, including my PhD peers, and have valued their encouragement, advice and support. Being situated within ISMH has brought with it opportunities for me to develop broader skills, including helping to organise a training session on time series methods, assisting in a rapid evidence review, peer reviewing a journal paper on nalmefene, writing a blog on pharmacological approaches to reducing alcohol consumption, and contributing to an online MSc in Substance Use. I am currently working on a study to explore the management of alcohol problems in primary care and have drafted a journal paper based on the role of marketing activities in influencing uptake of nalmefene (to be submitted).

There have been many challenges along the way. The mixed-methods approach has been challenging due to the wide variety of skills needed, including managing and making sense of the vast amount of data collected. I had to acquire new skills in managing and analysing GP data, time series analysis, qualitative interviewing and analysis, documentary research and analysis, critically appraising scientific papers, and mixed-methods research design, analysis

and interpretation. I have also developed new skills in utilising software packages including STATA, EXCEL, NVivo and PYTHON. Collecting and analysing data across the three study strands was time-consuming, involved three separate ethics applications, and a governance process to access and use the CPRD data.

The multi-disciplinary nature of this study has been challenging. To gain an understanding of nalmefene prescribing patterns and influences, I had to familiarise myself with the literature from diverse fields, including clinical trial conduct, alcohol treatment, pharmaceutical marketing, conflicts of interest and prescribing data. Having a non-clinical background meant that it took me some time to comprehend complex findings in clinical trials papers and to have the confidence to discuss these in writing and presentations.

Finally, and more generally, the challenge has been in the day-to-day practicalities of conducting the research. Bryman (2012, p. 15) writes about the 'messiness' of research, how things may not go according to the initial plan and how studies can run into "*false starts, blind alleys, mistakes and enforced changes to research plans*." In this study, I encountered many such challenges, including difficulties and delays in accessing patient-level data (for which a number of different sources and cost implications had to be investigated); a longer than expected time required for data management of the patient-level data; and difficulties and delays in identifying and recruiting individuals with sufficient knowledge of nalmefene, especially those from primary care. Consequently, I have had to adopt a pragmatic and flexible approach to the study, making changes to the scope of some strands and to the overall study order and timetable. A final and unexpected challenge resulted from COVID-19. For me, this has involved working from home and having to take on home-schooling commitments as a result of school closures. This, and being unable to have face-to-face support from supervisors and peers, has, at times, had an impact on my motivation and ability to focus on writing, and has caused delays in completing the thesis. Despite these challenges, I have learned so much on this PhD journey and have gained confidence in my abilities as a researcher.

8.7 Conclusion

Despite major limitations in the evidence base, wide-ranging marketing activities undertaken for nalmefene helped secure support for the drug and a place in UK alcohol treatment. Lundbeck's involvement in the scientific literature and the work of stakeholders presented

opportunities for bias in research outcomes and agendas, and in wider debates and decisions relating to alcohol treatment and policy. Although stronger transparency policies are required to ensure industry involvement in these activities is explicit, interventions to facilitate independence in research and health care decision-making are also required. Greater awareness of the mechanisms through which commercial influences can act is essential in developing such interventions, although there also needs to be willingness from policy makers to act.

The marketing strategies undertaken by the drug company failed to achieve a high uptake for nalmefene in UK primary care. A key barrier for nalmefene use related to the proposed model of delivery, which was incompatible with established ways of working in the current treatment system. Primary care prescribing of nalmefene did not appear to align well with the licensing conditions for the drug, presenting potential risks for patients and implications for health service resources. These findings on nalmefene expand knowledge about the challenges of implementing alcohol interventions in primary care and reiterate the need for researchers and those evaluating research evidence to consider the context of real world clinical practice – to account for not only the types of patients seen in practice but also how clinicians work, including their skills and attitudes.

Uncertainties remain about how best to support the large and diverse group of harmful and dependent drinkers to reduce their alcohol consumption. The case of nalmefene suggests that these are likely to be better resolved through publically funded rather than commercial research that includes the study of attitudes to treatment, current systems of treatment, how best to engage patients, as well as psychosocial interventions. Future interventions will also need to be implemented into routine clinical practice and the case of nalmefene highlights how challenging that can be, even with significant financial resources. Primary care may offer the most appropriate setting for identifying and engaging this group of drinkers. However, for primary care professionals to play a greater role in addressing the needs of dependent drinkers, and those with alcohol problems more generally, they need to be engaged in developing effective interventions that they are motivated to deliver, and adequately resourced to deliver them.

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Appendix 1: Systematic literature search strategy

A literature search was carried out on 13th June 2014, supplemented by a repeat search on 4 December 2014. A second identical search was carried out on 15th September 2017 to capture records published between June 2014 and September 2017. The following databases were searched:

- PubMed
- Cinahl via EBSCOHost
- HealthSource via EBSCOHost
- Web of Science Core Collection
- Google Scholar (UK)

Search strategy

PubMed and items returned in 2017 search (15/09/17):

Search	Query
#9	Search (#8 AND (2014/06/01:2017/12[crdt])) Sort by: PublicationDate
#8	Search (#4 OR #7)
#7	Search (#5 AND #6)
#6	Search (pubstatusaheadofprint OR (2016:2017[edat] OR 2016:2017[crdt] OR 2016:2017[dp]))
#5	Search (alcohol* AND (nalmefene* OR selincro))
#4	Search (#3 AND Humans[Mesh])
#3	Search (#1 AND #2)
#2	Search (Nalmefene OR Selincro OR nalmetrene)
#1	Search (("Alcohol Abstinence"[Mesh] OR "Alcohol Deterrents"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Alcoholic Beverages"[Mesh] OR "Alcoholic Intoxication"[Mesh] OR "Alcoholics"[Mesh] OR "Alcohol-Induced Disorders"[Mesh] OR "Alcoholism"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR "Binge Drinking"[Mesh]) OR alcohol*[TiAb])

Cinahl via EBSCOHost and items returned in 2017 search (15/09/17)

Search	Query	Limiters/Expanders
#4	#1 AND #2	Limiters - Published Date: 20140601-20171231 Search modes - Boolean/Phrase
#3	#1 AND #2	Search modes - Boolean/Phrase
#2	Nalmefene* OR Selincro OR nalmetrene	Search modes - Boolean/Phrase
#1	(MH "Alcohol-Related Disorders+") OR (MH "Alcohol Deterrents+") OR (MH "Alcohol Drinking+") OR (TI alcohol* OR AB alcohol*) OR (TI drinker# OR AB drinker#)	Search modes - Boolean/Phrase

HealthSource via EBSCOHost and items returned in 2017 search (15/09/17)

Search	Query	Limiters/Expanders
#4	#1 AND #2	Limiters - Published Date: 20140601-20171231 Search modes - Boolean/Phrase
#3	#1 AND #2	Search modes - Boolean/Phrase
#2	Nalmefene* OR Selincro OR nalmetrene	Search modes - Boolean/Phrase
#1	DE alcohol* OR TI alcohol* OR AB alcohol*	Search modes - Boolean/Phrase

Web of Science Core Collection and items returned in 2017 search (15/09/17)

Search	Query
#4	#3 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2014-2017
#3	#2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
#2	TS=(alcohol*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
#1	TS=(Nalmefene* OR Selincro OR nalmetrene) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Google Scholar UK and items returned in 2017 search (15/09/17)

All of these words:	This exact phrase:	Any of these words:	Limits:
Nalmefene alcohol	published online		2014-2017 Articles excluding patents and citations

Online trial registers

Searches were also made in online trial registers on 3rd December 2014 using the terms Nalmefene or Selincro (and repeated on 15th September 2017 for any records updated between 01/06/14 and 15/09/17):

- ClinicalTrials.gov
- European Union Clinical Trials Register
- International Standard Randomised Controlled Trial Number Register
- World Health Organization International Clinical Trials Registry Platform

Appendix 2: Nalmefene prescribing analysis: Additional tables

Table 1: Classification of practice type within the data

Type of practice	Number (%) of practices in dataset	Number (%) of prescribing entries for this group	Total (%) items prescribed by this group
Standard GP practice	1666 (94.9)	5275 (88.8)	7062 (81.3)
Community Health Services[1]	15 (0.9)	112 (1.9)	251 (2.9)
Public Health Services[1]	64 (3.6)	479 (8.1)	1250 (14.4)
Other[1]	11 (0.6)	75 (1.3)	120 (1.4)
All	1756	5941	8683

Source: OpenPrescribing.net, EBM DataLab, University of Oxford, 2017

1. For analytical purposes, Community Health Services, Public Health Services and Other services were combined to form one group 'Non-standard' practices.

Table 2: Monthly nalmefene prescribing – number of CCGs prescribing, number of standard GP practices prescribing, and number of prescription items prescribed (May 2013 to Jan 2017)

Month	CCGs	GP practices	Items
2013-05	6	6	6
2013-06	15	15	17
2013-07	16	19	23
2013-08	15	16	19
2013-09	10	11	11
2013-10	18	19	26
2013-11	15	17	19
2013-12	25	31	39
2014-01	24	27	38
2014-02	24	28	34
2014-03	26	29	39
2014-04	23	26	38
2014-05	26	29	44
2014-06	28	29	39
2014-07	30	33	44
2014-08	29	34	48
2014-09	32	37	58
2014-10	115	196	238
2014-11	117	202	253
2014-12	133	264	348
2015-01	111	214	289
2015-02	108	210	278
2015-03	113	206	273
2015-04	118	210	277
2015-05	108	206	262
2015-06	116	215	283
2015-07	119	225	308
2015-08	106	188	243
2015-09	105	179	241
2015-10	111	186	256

2015-11	101	193	248
2015-12	93	175	240
2016-01	93	172	229
2016-02	84	152	198
2016-03	76	135	194
2016-04	89	163	208
2016-05	82	148	193
2016-06	80	131	173
2016-07	74	134	163
2016-08	78	142	209
2016-09	84	148	207
2016-10	72	112	162
2016-11	80	129	183
2016-12	71	123	197
2017-01	71	111	167
All	206	1666	7062

Source: OpenPrescribing.net, EBM DataLab, University of Oxford, 2017

Table 3: Prescribing items by CCG area and practice type (May 2013 to Jan 2017)(highest ten prescribing CCGs presented)

CCG	Standard GP practices	Non-standard GP practices	Total nalmefene prescriptions
NHS Wiltshire	159	171	330
NHS Oldham	191		191
NHS Walsall	185		185
NHS St Helens	10	170	180
NHS Mid Essex	169		169
NHS Tameside & Glossop	168		168
NHS Northumberland	159		159
NHS Gloucestershire	129	4	133
NHS East Leicestershire & Rutland	127		127
NHS Kernow	121		121

Source: OpenPrescribing.net, EBM DataLab, University of Oxford, 2017

Table 4: Variables used in time series regression models

Model	Variable	Description
Model A	totalprescribinggen2	The dependent variable - number of monthly nalmefene items prescribed by all standard GP practices.
	Month_number	A number from 1 to 45 representing the month in which nalmefene was prescribed (from May 2013 to Jan 2017)
	Monthcentred	A variable derived using Month_number which accounts for each prescribing month relative to the intervention month (month 18; October 2014). Monthcentred therefore runs from -17 to +27. The intervention month is coded as monthcentred=0.

	Month1	Pre-intervention time point
	Month2	Post-intervention time point
	nice_1014	Intervention variable - the publication of NICE draft TA on 2nd October 2014. Coded as: 0=Pre-intervention (May13 to Sept14) 1=During and after the intervention (Oct14 to Jan17)
Model B	items	The dependent variable (monthly items prescribed) used in the mixed Poisson model of prescribing by all GP practices in the dataset (standard and non-standard practices)
	Month_number	As for Model A
	Monthcentred	As for Model A
	Month1	As for Model A
	Month2	As for Model A
	nice_1014	As for Model A
	min_prac_type	Recoded practice type variable. For the Poisson model this has been specified as a fixed effects covariate. Coded as: 1=Standard GP practices 2=Non-standard practices
	prac_ID3	A variable holding the unique ID code for an individual practice. For the Poisson model this has been specified as a random effects covariate.

Table 5: Durbinalt alternative test for serial correlation in the data

Durbinalt test on pre- and post-intervention data for standard GP practices

Data	Lags (p)	F	Df	Prob>F
Pre-intervention data	1	0.157	(1, 14)	0.6977
Post-intervention data	1	0.605	(1, 25)	0.4438

H0: no serial correlation

Table 6: Model A: The impact of the NICE TA on prescribing by 'standard' GP practices

a) Pre-intervention regression model output

Number of obs =17, F(1,15) = 87.21, Prob>F = 0.000, *R*-squared = 0.8532, Adj *R*-squared = 0.8435, Root MSE = 5.6299

Source	SS	df	MS
Model	2764.32353	1	2764.32353
Residual	475.441176	15	31.6960784
Total	3239.76471	16	202.485294

totalprescribinggen2	Coef.	SE	T	P>|t|	95% CI	
Monthcentred	2.602	0.2787	9.34	0.000	2.008	3.197
_cons	55.308	2.8560	19.37	0.000	49.221	61.396

b) Post-intervention regression model output

Number of obs =28, F(1,26) = 62.30, Prob>F = 0.000, *R*-squared = 0.7056, Adj *R*-squared = 0.6942, Root MSE = 26.113

Source	SS	df	MS
Model	42482.8134	1	42482.8134
Residual	17728.6152	26	681.8698
Total	60211.4286	27	2230.0529

totalprescribinggen2	Coef.	SE	T	P>|t|	95% CI	
Monthcentred	-4.8221	0.6109	-7.89	0.000	-6.077	-3.566
_cons	297.955	9.611	31.00	0.000	278.199	317.711

c) Combined regression model output

Number of obs =45, F(3,41) = 354.72, Prob>F = 0.000, *R*-squared = 0.9629, Adj *R*-squared = 0.9602, Root MSE = 21.071

Source	SS	df	MS
Model	472492.744	3	157497.581
Residual	18204.0564	41	444.0013
Total	490696.8	44	11152.2

totalprescribinggen2	Coef.	SE	T	P>|t|	95% CI	
nice_1014	242.646	13.206	18.37	0.000	215.975	269.318
nice_10141	0	(omitted)				
month1	2.602	1.043	2.50	0.017	0.496	4.709
month2	-4.822	0.492	-9.78	0.000	-5.817	-3.826
_cons	55.308	10.689	5.17	0.000	33.720	76.896

Testing difference in intercepts

totalprescribinggen2	Coef.	SE	T	P>|t|	95% CI	
(1)	242.646	13.206	18.37	0.000	215.975	269.318

Testing difference in slopes

totalprescribinggen2	Coef.	SE	T	P>|t|	95% CI	
(1)	-7.425	1.153	-6.44	0.000	-9.755	-5.094

Table 7: Model B: The impact of the NICE TA on prescribing by all practices: a mixed effects Poisson model

Mixed effects Poisson regression model output

Number of obs =79,020, Group variable: prac_ID3, Number of groups = 1,756
Obs per group: min=45, avg=45.0, max=45
Integration method: mvaghermite, Integration pts.=7, Wald chi2(4)=2556.43, Log likelihood=-23,096.067, Prob>chi2=0.0000

Items	IRR	SE	Z	P>|z	95% CI	
month_number	1.09343	0.0096	10.10	0.000	1.074	1.1125
1.nice_1014	29.1635	3.34750	29.39	0.000	23.288	36.521
nice_1014#c.month_number 1	0.903846	0.00808	-11.30	0.000	0.8881	0.9198
min_prac_type	0.309334	0.03452	-10.51	0.000	0.2485	0.3849
_cons	0.013504	0.00204	-28.46	0.000	0.0100	0.0182
Var(_cons)	0.88384	0.04024			0.8084	0.9664

Note: Estimates are transformed only in the first equation.
Note: _cons estimates baseline incidence rate (conditional on zero random effects).

Testing the efficiency of the model

A test of the efficiency of the mixed effects Poisson model compared with the standard Poisson regression suggests that the mixed effects model is better.

LR test vs. Poisson model: chibar2(01) = 8728.72 Prob>=0.0000

Table 8: List of patient files from CPRD used in the analysis

File	Description
Patient	Basic demographics and registration details
Practice	Practice details
Staff	Staff details
Consultation	Type of consultation
Clinical	Medical history events including symptoms, signs and diagnoses, coded using Read codes.
Additional Clinical Details	Additional details relating to symptoms, signs and diagnoses.
Referral	Information about patient referrals to external care centres (usually to secondary care locations such as hospitals for inpatient or outpatient care).
Therapy	Details of all prescriptions on the GP system.

Source: MHRA CPRD Gold Data Specification Document v1.9

Table 9: Alcohol dependence Read codes

Code	Code Description
8BA8.00	alcohol detoxification
8H35.00	admitted to alcohol detoxification centre
E010.00	Alcohol withdrawal delirium
E010.12	Delirium tremens
E012000	Chronic alcoholic brain syndrome
E013.00	Alcohol withdrawal hallucinosis
E01y000	Alcohol withdrawal syndrome
E23..00	Alcohol dependence syndrome
E230.00	Acute alcoholic intoxication in alcoholism
E230000	Acute alcoholic intoxication; unspecified; in alcoholism
E230100	Continuous acute alcoholic intoxication in alcoholism
E230.11	Alcohol dependence with acute alcoholic intoxication
E230300	Acute alcoholic intoxication in remission; in alcoholism
E230z00	Acute alcoholic intoxication in alcoholism NOS
E231.00	Chronic alcoholism
E23..11	Alcoholism
E231100	Continuous chronic alcoholism
E231.11	Dipsomania
E231300	Chronic alcoholism in remission
E231z00	Chronic alcoholism NOS
E23z.00	Alcohol dependence syndrome NOS
Eu10200	[X]Mental and behavioural disorders due to use of alcohol: dependence syndrome
Eu10211	[X]Alcohol addiction
Eu10212	[X]Chronic alcoholism
Eu10213	[X]Dipsomania
Eu10300	[X]Mental and behavioural disorders due to use of alcohol: withdrawal state
Eu10400	[X]Mental and behavioural disorders due to use of alcohol: withdrawal state with delirium
Eu10411	[X]Delirium tremens; alcohol induced
Eu10712	[X]Chronic alcoholic brain syndrome
Eu10800	[X]Alcohol withdrawal-induced seizure
F11x000	Cerebral degeneration due to alcoholism
F11x011	Alcoholic encephalopathy
F375.00	Alcoholic polyneuropathy
F394100	Alcoholic myopathy
G555.00	Alcoholic cardiomyopathy
J612.00	Alcoholic cirrhosis of liver
J617000	Chronic alcoholic hepatitis
J671000	Alcohol-induced chronic pancreatitis
Z191.00	Alcohol detoxification

Source: Thompson et al., 2017. See published codelist at Clinical codes: https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/58/

Table 10: Harmful drinking Read codes

Code	Code Description
1364	Moderate drinker - 3-6u/day
1365	Heavy drinker - 7-9u/day
136K.00	Alcohol intake above recommended sensible limits
1366	Very heavy drinker - >9u/day
136R.00	Binge drinker
E23..12	Alcohol problem drinking
136T.00	Harmful alcohol use
136S.00	Hazardous alcohol use
136O.00	Moderate drinker
136P.00	Heavy drinker
E250.00	Nondependent alcohol abuse
136Q.00	Very heavy drinker
136a.00	Increasing risk drinking
136W.00	Alcohol misuse
136Y.00	Drinks in morning to get rid of hangover
136b.00	Feels should cut down drinking
136c.00	Higher risk drinking
1462	H/O: alcoholism
E230200	Episodic acute alcoholic intoxication in alcoholism
E231000	Unspecified chronic alcoholism
E231200	Episodic chronic alcoholism
E250000	Nondependent alcohol abuse, unspecified
E250100	Nondependent alcohol abuse, continuous
E250200	Nondependent alcohol abuse, episodic
E250300	Nondependent alcohol abuse in remission
E250z00	Nondependent alcohol abuse NOS
Eu10100	[X]Mental and behav dis due to use of alcohol: harmful use
ZV11300	[V]Personal history of alcoholism
8CAM	Patient advised about alcohol

Table 11: Psychosocial Support Read codes

Code	Code Description
13Y8.00	Alcoholics anonymous
66e0.00	Alcohol abuse monitoring
7P22100	Delivery of rehabilitation for alcohol addiction
8CAv.00	Advised to contact primary care alcohol worker
8H7p.00	Referral to community alcohol team
8HHe.00	Referral to community drug and alcohol team
8HkG.00	Referral to specialist alcohol treatment service
8HkJ.00	Referral to alcohol brief intervention service
8IAF.00	Brief intervention for excessive alcohol consumption declined
8IAJ.00	Declined referral to specialist alcohol treatment service
8IAt.00	Extended intervention for excessive alcohol consumption declined

8IEA.00	Referral to community alcohol team declined
9k1..00	Alcohol misuse - enhanced services administration
9k11.00	Alcohol consumption counselling
9k12.00	Alcohol misuse - enhanced service completed
9k14.00	Alcohol counselling by other agencies
9k1A.00	Brief intervention for excessive alcohol consumption completed
9k1B.00	Extended intervention for excessive alcohol consumption completed
9NN2.00	Under care of community alcohol team
Z191100	alcohol withdrawal regime
Z191211	alcohol reduction programme
Z4B1.00	Alcoholism counselling
ZV57A00	[V]Alcohol rehabilitation
ZV6D600	[V]Alcohol abuse counselling and surveillance

Source: Thompson et al., 2017. See published codelist at Clinical codes: https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/58/

Table 12: List of medications for alcohol problems

Medication	Product names	CRPD product code
Nalmefene	Nalmefene 18mg Selincro 18mg	56720 57225
Acamprosate	Acamprosate 333mg Campral EC 333mg	2598 6759
Disulfiram	Disulfiram 200mg Antabuse 200mg	871 2269
Naltrexone	Naltrexone 50mg Nalorex 50mg	6755 18073
Baclofen	Baclofen 10mg Lioresal 10mg	1197 2715
Topiramate	Topiramate 25mg tablets Topiramate 25mg capsules Topiramate 50mg	11237 5874 7073
Chlordiazepoxide	Chlordiazepoxide 10mg capsules Chlordiazepoxide 10mg tablets Chlordiazepoxide 5mg capsules Chlordiazepoxide 5mg tablets Librium 10mg capsules Librium 5mg capsules	1463 5294 2122 6025 24599 18125

Table 13: Codes indicating alcohol detoxification treatment

Code	Code description
8H35.00	Admitted to alcohol detoxification centre
8BA8.00	Alcohol detoxification

Table 14: List of medications used to identify comorbidity relating to alcohol problems

Medication group and name	Product names and CPRD code
SSRIs[1]	
Fluoxetine	Fluoxetine 10mg (67463) Fluoxetine 20mg (22) Fluoxetine 60mg (4075) Prozac 20mg (418) Prozac 60mg (4907)
Paroxetine	Paroxetine 10mg (35021) Paroxetine 20mg (34351) Paroxetine 20mg (50) Paroxetine 30mg (1397) Paroxetine 10mg/5ml oral suspension (527) Seroxat 20mg (841)
Citalopram	Citalopram 10mg (476) Citalopram 20mg (67) Citalopram 40mg (4770) Cipramil 10mg (3861) Cipramil 20mg (1712) Cipramil 40mg (2408)
Escitalopram	Escitalopram 5mg (6405) Escitalopram 10mg (306) Escitalopram 20mg (6218) Cipralex 5mg (785) Cipralex 10mg (648) Cipralex 20mg (6360)
Sertraline	Setraline 50mg (488) Sertraline 100mg (727) Lustral 50mg (1612)
Fluvoxamine	Faverin 100mg (12123)
Anti-Ulcer drugs[2]	
Ranitidine	Ranitidine 150mg (21) Ranitidine 300mg (1556) Zantac 150mg (1229) Zantac 300mg (7666)
Omeprazole	Omeprazole 10mg gastro-resistant tablets (89) Omeprazole 20mg gastro-resistant capsules (18) Omeprazole 40mg gastro-resistant capsules (1451) Omeprazole 10mg disposable gastro-resistant tablets (5232) Omeprazole 20mg disposable gastro-resistant tablets (4921) Losec 10mg gastro-resistant capsules (276)

Esomeprazole	Losec 20mg gastro-resistant capsules (1232) Losec MUPS 40mg gastro-resisant tablets (9825) Esomeprazole 20mg gastro-resistant capsules (43995) Esomeprazole 20mg gastro-resistant tablets (5178) Esomeprazole 40mg gastro-resistant tablets (5604) Nexium 20mg gastro-resistant tablets (5269) Nexium 40mg gastro-resistant tablets (6490)
Pantoprazole	Pantoprazole 20mg gastro-resistant tablets (5419) Pantoprazole 40mg gastro-resistant tablets (1986)
Lansoprazole	Lansoprazole 15mg gastro-resistant capsules (30) Lansoprazole 15mg orodispersible tablets (6245) Lansoprazole 30mg gastro-resistant capsules (39) Lansoprazole 30mg orodispersible tablets (6300)
Diazepam	Diazepam 2mg tablets (45, 33672, 34335) Diazepam 5mg tablets (47) Diazepam 10mg tablets (1400)

1. The list of SSRIs was informed by the SSRI drugs listed on OpenPrescribing.net – see https://openprescribing.net/bnf/0403/ Patient records were also searched for Dapozetine/Priligy but none were found.
2. The list of anti-ulcer drugs was informed by those most commonly prescribed, based on NHS website (https://www.nhs.uk/conditions/stomach-ulcer/treatment/) and NICE guidelines (https://pathways.nice.org.uk/.../managing-peptic-ulcer-disease-in-adults)

Table 15: Codes used to define liver problems

Code	Code Description
14C5.00	H/O: liver disease
J61z.00	Chronic liver disease NOS
J625.11	[X] Liver failure
R148.00	[D]Abnormal liver function test
J613.00	Alcoholic liver damage unspecified
J610.00	Alcoholic fatty liver
J612.00	Alcoholic cirrhosis of liver
J61..00	Cirrhosis and chronic liver disease
J615z13	Cirrhosis of liver NOS
J63..00	Other liver disorders
9N0v.00	Seen in liver clinic
J617.00	Alcoholic hepatitis
J611.00	Acute alcoholic hepatitis

Table 16: Consultation type groupings

Consultation type	Consultations included
Face to face	Clinic
	Night visit, Deputising service
	Follow-up/routine visit
	Night visit, Local rota
	Night visit , practice
	Out of hours, Practice
	Out of hours, Non Practice

	Surgery consultation
	Acute visit
	Children's Home Visit
	Home Visit
	Hotel Visit
	Nursing Home Visit
	Residential Home Visit
	Twilight Visit
	Walk-in Centre
	Co-op Surgery Consultation
	Co-op Home Visit
	Community Clinic
	Night Visit
Telephone	Telephone call from a patient
	Telephone call to a patient
	Co-op Telephone advice
	Telephone Consultation
Other - mail or email	Mail/email
	Mail from patient
	Mail to patient
Other referral/third party	Third Party Consultation
	General Ophthalmic Services (GOS) 18 Report
	Discharge details
	Letter from Outpatients
	Day Case Report
	NHS Direct Report
	Community Nursing Note
	Community Nursing Report
	Health Visitor Note
	Health Visitor Report
	Hospital Inpatient Report
	Laboratory Request
	Radiology Request
	Radiology Result
	Referral Letter
	Social Services Report
	GP to GP communication transaction
Other secondary care episode	Secondary care episode
	Casualty Attendance
	Hospital Admission
	Minor Injury Service
Other Admin	Administration
	Data Transferred from other system
	Health Authority Entry

	Template Entry
Other unknown	Repeat Issue
	Other
	Results recording
	Emergency Consultation
	Triage
	Medicine Management
	Initial Post Discharge Review
	Non-consultation medication data
	Non-consultation data

Source: Kontopantelis et al., 2015b

Table 17: Receipt of prescriptions for other alcohol medications (pre-and post-nalmefene)

Drug	% of nalmefene patients prescribed the drug pre-nalmefene	% of nalmefene patients prescribed the drug post-nalmefene
Disulfiram	5.4	5.4
Acamprosate	24.5	10.7
Naltrexone	2.7	1.5
Baclofen	2.7	1.9
Topiramate	1.1	0.0
Any AD drug	29.9	16.1
Chlordiazepoxide	24.0	12.6
Base	261	261

Table 18: List of staff roles used to define contact with a GP or practice nurse

GP or Practice Nurse Staff roles included
Associate
Consultant
GP Registrar
GP Retainer
Locum
Partner
Salaried Partner
Senior Partner
Practice Nurse

Table 19: Results of paired samples t-test for changes in the level of GP contact pre and post-first nalmefene prescription

```
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
F2FTE~tN |     211    7.810427    .5122824    7.441332    6.800552    8.820302
F2FTE~eN |     211    7.279621    .3663979    5.322237    6.557332     8.00191
---------+--------------------------------------------------------------------
    diff |     211    .5308057    .5067932    7.361596   -.4682482     1.52986
------------------------------------------------------------------------------
     mean(diff) = mean(F2FTELeventsb~tN - F2FTELeventsb~eN)       t =   1.0474
 Ho: mean(diff) = 0                               degrees of freedom =      210

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.8519         Pr(|T| > |t|) = 0.2961          Pr(T > t) = 0.1481
```

Table 20: Quantity of tablets in first nalmefene prescription

First quantity prescribed (number of tablets)	% of nalmefene patients
1	0.4
7	1.9
14	51.0
28	46.4
56	0.4
Mean	*20.47*
SD	*7.6*
Median	*14*
Mode	*14*
Base	261

Table 21: Rates of usage of nalmefene

Rates of usage of nalmefene	% of all nalmefene patients	% of patients with 6 or more prescriptions
>0 to <=0.3	17.9	25.0
>=0.4 to<=0.6	20.0	10.0
>=0.7	62.1	65.0
Mean	*0.7*	*0.7*
Median	*0.7*	*0.8*
SD	*0.4*	*0.3*
Base	95	20

Table 22: Pre-nalmefene assessment of patients

Consultation received 2 to 4 weeks prior to first nalmefene prescription	Number of nalmefene patients	%
Any consultation type	184	70.5
Face-to-face or telephone consultation	104	39.8
Base (all nalmefene patients)	261	100.0

Note: assumes an average of 30 days per month

Table 23: Follow up of nalmefene patients

Face-to-face or telephone consultations after first nalmefene prescription	Number of nalmefene patients	%
At least one in the first month since nalmefene prescription	153	58.6
At least one in the first 2 months since nalmefene prescription	187	71.6
Base (all nalmefene patients)	261	100.0

Note: assumes an average of 30 days per month

Table 24: Comparison of nalmefene patients with RCT and licensed population

Patient characteristics	Nalmenfene patients	RCTs/Licensing conditions
Mean age	50	Ranges from 44-52
Gender	58% male; 42% female	Trial population ranges from 66-75% male
Alcohol consumption/DRL	35% of patients with a high DRL	Majority drinking at least at a High DRL (77% for Esense1; 80% for Esense2; 52% for Sense)
Alcohol dependence diagnosis	43% of patients with a Read code recorded prior to their nalmefene prescription.	All trial patients had a primary diagnosis of alcohol dependence (based on DSM-IV-TR)
Receipt of adjunct psychosocial support	8% of patients with a Read code indicating psychosocial support alongside their nalmefene prescription (within a 3-month period either side of prescription date)	All clinical trials patients received psychosocial support provided alongside their nalmefene.
Pre-nalmefene assessment	70% of patients received a consultation of some form 2-4 weeks prior to their nalmefene prescription; 40% had received a face-to-face or telephone consultation.	All clinical trials patients were assessed at baseline and 2 weeks later to check if they were still drinking at a high DRL.
Previous treatment for alcohol dependence (AD)	30% prescribed an AD drug prior to nalmefene; 50% with any prior alcohol treatment recorded (prescribed an AD drug, prescribed chlordiazepoxide, had a medical Read code for alcohol detox, or had a medical Read code indicating psychological support for alcohol problems)	30% of the trials population patient had previously engaged with 'treatment' for their alcohol dependence.[1]
Comorbidity	38% of nalmefene patients had been in receipt of an SSRI anti-depressant medication within the three months prior to receiving nalmefene.	Patients with certain comorbid disorders were excluded from the RCTs – in ESENSE 1 and 2, they were excluded if they had a DSM-IV Axis I disorder other than alcohol or nicotine dependence or if they reported 'current or recent' treatment

		with antipsychotics or antidepressants.
Recent prescriptions for alcohol treatment	9.2% of patients had received a prescription for another AD drug three months prior to nalmefene. 7.3% had received a prescription for chlordiazepoxide within this time period.	Patients excluded from ESENSE 1 and 2 trials if current or recent (within 3 months preceding screening) treatment with disulfiram, acamprosate, topiramate or carbimide, or with any opioid antagonist.
Usage rate	Nalmefene used on an average of 70% of days	Nalmefene used on an average of 50% of days (ESENSE 1), 57% of days (ESENSE 2) and 48% of days (SENSE)
Setting	Patients treated in UK primary care	Only 1 of the three trials (SENSE) recruited UK patients. None of the trials recruited patients from the primary care setting.
Duration of nalmefene treatment	12% of patients received nalmefene prescriptions 6 months on from their initial prescription; 5% were receiving it at 12 months	6 months trial period for ESENSE 1 and 2 trials; 12 months for SENSE

1. No definition for 'treatment' is provided.

Box 1: Example Python programming code to extract latest recorded alcohol units for each patient prior to their nalmefene prescription

```
import pandas as pd

def get_most_recent_units(df):
    return df[~df['Data 2'].isnull()].sort_values('eventdate')[['eventdate', 'DateN', 'Data 2']].tail(1)

df = pd.read_excel('Clinical file for max units among N patients.xlsx', sheet_name=0,
engine='openpyxl')

#Get most recent units pre-nalm. enttype 5 = Alcohol, DateN is date Nalmefene was prescribed

df_pre = df[(df['enttype'] == 5) & (df['eventdate'] <= df['DateN'])]
df_pre_nalm = df[(df['enttype'] == 5) & (df['eventdate'] <= df['DateN'])]
df_most_recent_pre_nalm = df_pre.groupby('patid').apply(get_most_recent_units)
df_most_recent_pre_nalm['datediff'] = (
    df_most_recent_pre_nalm['DateN'] - df_most_recent_pre_nalm['eventdate']
).dt.days
df_most_recent_pre_nalm.to_csv('Most recent units pre nalm.csv')
```

Appendix 3: Tables for documentary analysis

Table 1: Scientific papers

	Title/Author	Date	Type[1]	Main focus[2]	Conclusion on nalmefene[2]	Critical discussion of RCTs[2]	Supportive Themes[2]	Overall support grading[2]	COIs[2]	Funding[2]
1	Mann et al. Extending the treatment options in alcohol dependence: A randomised controlled study of as-needed nalmefene. *Biological Psychiatry*, 73(8), 706-713.	2013	OT	1	1	1	1,3,4,9	2	1	1
2	Gual et al. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. *European Neuropsychopharmacology*, 23(11), 1432-1442.	2013	OT	1	1	1	1,2,3,4,9	2	1	1
3	van den Brink et al (a). Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. *Journal of Psychopharmacology*, 28(8), 733-744.	2014	OT	1,2	1	1	2,9	2	1	1
4	van den Brink et al. Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level: Results from a subgroup analysis of two randomised controlled 6-month studies (vol 48, pg 570, 2013). *Alcohol and Alcoholism*, 48(6), 746-746.	2013	SA	1	1	1	9	2	1	1
5	Laramée et al. The cost-effectiveness and public health benefit of nalmefene added to psychosocial support for the reduction of alcohol consumption in alcohol-dependent patients with high/very high drinking risk levels: A Markov model. *BMJ Open*, 4(9), e005376-2014-005376.	2014	SA	3	1	1	1,3,7,8,9	2	1	1
6	Sinclair et al. Can alcohol dependent patients adhere to an 'As-needed 'medication regimen? *European Addiction Research*, 20(5), 209-217.	2014	SA	5	1	2	4,5,9,11	1	1	1

7	Francois et al. A predictive microsimulation model to estimate the clinical relevance of reducing alcohol consumption in alcohol dependence. *European Addiction Research*, 20(6), 269-284.	2014	SA	4	1	2	6,8,9	1	1	1
8	Aubin et al. Clinical relevance of as needed treatment with nalmefene in AD patients. *European Addiction Research* 2015; 21:160-168	2015	SA	4	1	1	2,4,6,8,9	2	1	1
9	Roerecke et al. Clinical relevance of nalmefene versus placebo in alcohol treatment: Reduction in mortality risk. *Jnl of Psychopharmacology* 2015. Vol. 29(11) 1152-1158	2015	SA	4	1	2	6,8,9	1	1	1
10	François et al. The effects of as-needed nalmefene on patient-reported outcomes and quality of life in relation to a reduction in alcohol consumption in alcohol-dependent patients. *PLoS One 2*015 Jun 8;10(6):e0129289	2015	SA	3	1	1	2,8,9	2	1	1
11	Van den Brink et al. Safety and tolerability of as-needed nalmefene in the treatment of alcohol dependence; results from the Phase III clinical programme. *Expert opinion on drug safety*. Vol14 No4 Pages 495-504	2015	SA	2	1	1	1,9	2	1	1
12	Brodtkorb et al. The cost effectiveness of nalmefene for reduction of alcohol consumption in alcohol-dependent patients with high or very high drinking-risk levels from a UK societal perspective. *CNS Drugs* (2016) 30:163–177	2016	SA	3	1	2	7,8,9	1	1	1
13	Laramée et al (a). The cost-effectiveness of the integration of nalmefene within the UK healthcare system treatment pathway for alcohol dependence. *Alcohol and Alcoholism*, Volume 51, Issue 3, 1 May 2016, Pages 283–290.	2016	SA	3	1	2	3,7,8,9	1	1	1
14	Laramée et al (b). A trial-based predictive microsimulation assessing the public health benefits of nalmefene and psychosocial support for the reduction of alcohol consumption in alcohol dependence. *Appl Health Econ Health Policy* (2016) 14:493–505	2016	SA	3	1	1	6,8,9	2	1	1

15	Rösner et al. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev*. 2010 Dec 8;(12):CD001867.	2010	SR/MA	6	2	1	NA	3	1	2
16	Jonas et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings A systematic review and meta-analysis. *JAMA: Journal of the American Medical Association*, 311(18), 1889-1900.	2014	SR/MA	6	1	1	NA	2	2	2
17	Palpacuer et al. 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 RCTs. *PLoS Medicine* December 22, 2015	2015	SR/MA	1	2	1	NA	3	1	2
18	Fitzgerald et al. Weak evidence on nalmefene creates dilemmas for clinicians and poses questions for regulators and researchers. *Addiction* Volume111, Issue 8 August 2016 Pages 1477-1487.	2016	SR/MA	1	2	1	NA	3	2	2
19	Naudet et al. Evaluation in alcohol use disorders – insights from the nalmefene experience. *BMC Medicine* (2016a) 14:119	2016	SR/MA	1	2	1	NA	3	1	2
20	Barrio, P. and Gual. A. Patient-centred care interventions for the management of AUDs: a systematic review of RCTs. *Patient preference and adherence* Vol 10 Pages 1823-1845.	2016	SR/MA	8	1	2	4,5,9,11	1	1	1
21	Mann et al. Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis on its clinical efficacy. *European Neuropsychopharmacology* Vol 26 No.12: 1941-1949	2016	SR/MA	1	1	1	2,8,9,11	2	1	2
22	Soyka et al. Comparing nalmefene and naltrexone in alcohol dependence: Are there any differences? Results from an indirect meta-analysis. *Pharmacopsychiatry* Vol 49 No2 Pages 66-75	2016	SR/MA	1	1	2	4,9	1	1	1

23	Soyka et al. Guidelines for biological treatment of substance use and related disorders, part 1: Alcoholism, first revision, *The World Journal of Biological Psychiatry*, 18:2, 86-119.	2017	SR/MA	6	1	2	11	1	1	2
24	Palpacuer et al. Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network meta-analyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate. *Addiction* 2018 Vol 113 Issue 2 220-237.	2017	SR/MA	6,7	2	1	NA	3	1	2
25	Aubin, H. & Daeppen, J. Emerging pharmacotherapies for alcohol dependence: A systematic review focusing on reduction in consumption. *Drug & Alcohol Dependence,* 133(1), 15-29.	2013	Other SR/MA	6,7	1	2	9,11	1	1	1
26	Sinclair et al. Safety and tolerability of pharmacological treatment of alcohol dependence: Comprehensive review of evidence. *Drug Saf* (2016) 39: 627.	2016	Other SR/MA	2	1	2	11	1	1	2
27	Johansen et al. Harms associated with taking nalmefene for substance use and impulse control disorders: A systematic review and meta-analysis of RCTs. PLoS ONE 12(8): e0183821.	2017	Other SR/MA	2	2	1	NA	3	2	2
28	Allen, D. Depression, excessive alcohol consumption and nalmefene. *Progress in Neurology and Psychiatry* Vol 18, No.5: 14-15	2014	Other N	1	1	2	9	1	2	2
29	Owens et al. Nalmefene in supporting alcohol reduction: observations from a clinical cohort. *Jnl of Addiction Medicine and Therapy* 3 (1): 1012	2015	Other N	1	1	2	1,9,10,11	1	1	2
30	Di Nicola et al. Nalmefene in alcohol use disorder subjects with psychiatric comorbidity: A Naturalistic Study. *Adv Ther* 34, 1636–1649 (2017).	2017	Other N	1	1	2	2,3,4,9,11	1	2	1
31	Soyka, M. & Rosner, S. Emerging drugs to treat alcoholism. *Expert Opinion on Emerging Drugs*, 15(4), 695-711.	2010	NR	6	1	3	12	6	4	3

32	Soyka, M. & Rosner, S. Nalmefene for treatment of alcohol dependence. *Expert Opinion on Investigational Drugs*, 19(11), 1451-1459.	2010	NR	1	1	3	12	6	4	3
33	Hillemacher et al. Opioid modulators for alcohol dependence. *Expert Opinion on Investigational Drugs*, 20(8), 1073-1086.	2011	NR	6	1	3	12	6	2[3]	2[3]
34	Yancey, J.R. & Lumbad, J. Opioid antagonists for the treatment of alcohol dependence. *American Family Physician*, 84(9), 990-992	2011	NR	6	2	2	NA	2	3	2
35	Forray, A. & Sofuoglu, M. Future pharmacological treatments for substance use disorders. *British Journal of Clinical Pharmacology*, 77(2), 382-400.	2014	NR	6	1	2	11	1	2	2
36	Kranzler, H. R. & McKay, J. R. Personalised treatment of alcohol dependence. *Current Psychiatry Reports*, 14(5), 486-493.	2012	NR	8	1	2	5,11	1	1	2
37	van Amsterdam, J. & van den Brink, W. Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. *Journal of Psychopharmacology*, 27(11), 987-997.	2013	NR	7	1	2	5,9	1	1	2
38	Keating, G. M. Nalmefene: A review of its use in the treatment of alcohol dependence. *CNS Drugs*, 27(9), 761-772.	2013	NR	1	1	2	2,4,9	1	5[4]	4[4]
39	Niciu, M. J. & Arias, A. J. Targeted opioid receptor antagonists in the treatment of alcohol use disorders. *CNS Drugs*, 27(10), 777-787.	2013	NR	6	1	1	4,9,11	2	2	2
40	Franck, J. & Jayaram-Lindstrom, N. Pharmacotherapy for alcohol dependence: Status of current treatments. *Current Opinion in Neurobiology*, 23(4), 692-699.	2013	NR	6	1	2	9,11	1	3	5
41	Williams et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *The Lancet* Vol 384 November29, 2014	2014	NR	9	3	2	NA	4	2	2
42	Nalmefene. Alcohol Dependence. No advance. *Prescrire International* 2014 23(150):150-152.	2014	NR	1	2	1	NA	3	2	2

43	Park, T.W. & Friedman, P.D. Medications for alcohol treatment: an opportunity for prescribing clinicians to facilitate remission from alcohol and opioid use disorders. *Rhode Island Medical Journal* (2013). 2014 Oct 1;97(10):20-24.	2014	NR	6	1	2	11	1	3	2
44	Evren, C. Nalmefene for reduced-risk drinking: it is not only fancy term for harm reduction. *Düşünen Adam The Journal of Psychiatry and Neurological Sciences* 2014;27:275-280.	2014	NR	1	1	2	9,11	1	3	5
45	Leeman et al. "Killing two birds with one stone": Alcohol use reduction interventions with potential efficacy in enhancing self-control. *Current Addiction Reports*, 1(1), 41-52.	2014	NR	7	1	2	9	1	2	2
46	Lin, S. Pharmacological means of reducing human drug dependence: A selective and narrative review of the clinical literature. *British Journal of Clinical Pharmacology*, 77(2), 242-252.	2014	NR	6	1	2	9,11	1	2	2
47	Muller et al. Current pharmacological treatment approaches for alcohol dependence. *Expert Opinion on Pharmacotherapy*, 15(4), 471-481.	2014	NR	6	5	3	12	6	4	3
48	Wackernah et al. Alcohol use disorder: Pathophysiology, effects, and pharmacologic options for treatment. *Substance Abuse and Rehabilitation*, 5, 1.	2014	NR	6	2	1	9,11	3	2	2
49	Luquiens, A. & Aubin, H.J. Patient preferences and perspectives regarding reducing alcohol consumption: Role of nalmefene. *Patient Preference and Adherence*, 8, 1347-1352.	2014	NR	1	1	2	1,4,5,9	1	1	2
50	Zindel, L.R. & Kranzler, H.R. Pharmacotherapy of alcohol use disorders: Seventy-five years of progress. *Journal of Studies on Alcohol and Drugs.Supplement*, 75 Suppl 17, 79-88	2014	NR	6	1	2	11	1	3	5
51	Keating, G. Nalmefene: A guide to its use in alcohol dependence. *Drugs & Therapy Perspectives*, 30(1), 10-15.	2014	NR	1	1	2	1,2,4	1	5[4]	4[4]
52	Gual et al. Nalmefene and its use in alcohol dependence (vol 50, pg 347, 2014). *Drugs of Today*, 50(9), 659-659.	2014	NR	1	1	2	1,4,9	1	1	2

53	Soyka, M. Nalmefene for the treatment of alcohol dependence: A current update. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, 17(4), 675-684.	2014	NR	1	1	1	1,4,9,11	2	1	2
54	Paille, F. & Martini, H. Nalmefene: A new approach to the treatment of alcohol dependence. *Substance Abuse and Rehabilitation*, 5, 87-94.	2014	NR	1	1	2	1,4,9	1	1[5]	2
55	Metz et al. Substance abuse/dependence treatment: A European perspective. *Substance Abuse*, 2014;35(3):309-20	2014	NR	8	1	2	3	1	3	5
56	Caputo et al. Pharmacological management of alcohol dependence: From mono-therapy to pharmacogenetics and beyond. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*, 24(2), 181-191.	2014	NR	6	1	2	9,11	1	1	2
57	Woody, G.E. Antagonist models for treating persons with substance use disorders. *Current Psychiatry Reports*, 16(10), 489.	2014	NR	6	1	2	11	1	2	2
58	Testino et al. Treatment of alcohol dependence: Recent progress and reduction of consumption. *Minerva Medica*, 105(6), 447-466.	2014	NR	7	1	3	12	6	1	1
59	Nutt, D. The role of the opioid system in alcohol dependence. *Jnl of Psychopharmacology* Vol28 No1 Pages: 8-22	2014	NR	6	1	2	11	1	1	2
60	Tyburski et al. New diagnostic criteria for alcohol use disorders and novel treatment approaches – 2014 update. *Archives of medical science*, 2014 Dec 22; 10(6): 1191–1197	2014	NR	8	3	2	9	4	3	5
61	Nutt, D. & Rehm, J. Doing it by numbers: a simple approach to reducing the harms of alcohol. *Jnl of Psychopharmacology* Vol 28 No 1:pages 3-7	2014	NR	7	1	2	9,11	1	1	2
62	Serecigni, J.G. Opioid receptor antagonists in the treatment of alcoholism. *Adicciones* 2015 Sep 29;27(3):214-230.	2015	NR	6	1	2	4,9,11	1	1	2

63	Garcia et al. Alcohol liver disease: A review of current therapeutic approaches to achieve long-term abstinence. *World Jnl Gastroenterology* 2015 July 28;21(28):8516-8526.	2015	NR	9	1	2	9	1	2	2
64	Yumoto, Y. & Higuchi, S. Pharmacological therapies for alcohol use disorder in Japan. *Nihon rinsho.Japanese journal of clinical medicine* Sep;73(9):1536-1539.	2015	NR	6	5	3	12	6	4	3
65	Tobutt, C. Alcohol: brief interventions for hazardous drinking and dependency. *British Journal of Mental Health Nursing* 2015;4(2):87-93.	2015	NR	8	1	2	9	1	3	5
66	Marazziti et al. Nalmefene A novel drug for an old disorder. *Current Medicinal Chemistry* 2015; 22(27): 3162-3168	2015	NR	1	1	3	1	6	4	3
67	Guardia-Serecigni, J. The reduction of alcohol consumption. A new treatment target for low-severity alcoholism. *Adicciones* Vol 27 No. 1 p:3-7	2015	NR	7	1	2	9,11	1	1	2
68	Thompson et al. Pharmacotherapy for alcohol dependence: A stratified approach. *Pharmacology and Therapeutics* 2015 Sep;153:10-24	2015	NR	6	1	1	11	2	1^{5}	2
69	Soyka, M. & Lieb, M. Recent development in pharmacotherapy of alcoholism. *Pharmacopsychiatry* Vol 48 No 4-5 Pages: 123-35	2015	NR	6	1	2	2,11	1	1	2
70	Michalak, A. & Biala, G. Alcohol dependence – neurobiology and treatment. *Acta Pol Pharm* 2016 Jan-Feb; 73(1): 3-12	2015	NR	6	1	2	11	1	3	5
71	Swift, R.M. & Aoun, E.G. Pharmacotherapy of Alcohol and Drug Dependence. *Curr Behav Neurosci Rep* 2, 30–39 (2015).	2015	NR	6	1	2	11	1	1	2
72	Soyka, M. & Mutschler, J. Treatment-refractory substance use disorder: Focus on alcohol, opioids and cocaine. *Progress in Neuropsychopharmacology and Biological Psychiatry* 2016 Oct 3;70:148-161.	2016	NR	6	1	2	11	1	1	2
73	Koob, G.F. & Mason, B.J. Existing and future drugs for the treatment of the dark side of addiction. *Annual Review of Pharmacology and Toxicology* 2016;56:299-322	2016	NR	6	5	3	12	6	4	3

74	Agabio et al. F. Efficacy of medications approved for the treatment of alcohol dependence and alcohol withdrawal syndrome in female patients: A descriptive review. *European Addiction Research* 2016; 22(1):1-16.	2016	NR	6	1	1	11	2	2	2
75	Batra et al. Alcohol dependence and harmful use of alcohol - diagnosis and treatment options. *Dtsch Artztebl Int* 2016; 113: 301-10.	2016	NR	8	1	2	9	1	1	2
76	Litten et al. Potential medications for the treatment of alcohol use disorder: An evaluation of clinical efficacy and safety. *Substance Abuse*, 37:2, 286-298.	2016	NR	6	1	2	11	1	2	2
77	Rolland et al. Pharmacotherapy for Alcohol Dependence: The 2015 Recommendations of the French Alcohol Society, Issued in Partnership with the European Federation of Addiction Societies. *CNS Neuroscience & Therapeutics* 22 (2016) 25-37	2016	NR	6	1	2	1,9,11	1	1	1
78	Soyka, M. Nalmefene for the treatment of alcohol use disorders: recent data and clinical potential. *Expert Opinion on Pharmacotherapy* Vol17 No4 Pages: 619-626	2016	NR	1	1	1	1,4,9,11	2	1	2
79	Mann et al. German guidelines on screening, diagnosis and treatment of alcohol use disorders. *European Addiction Research* 2017;23(1):45-60.	2017	NR	8	1	2	11	1	1	2
80	Burton et al. A rapid evidence review of the effectiveness and cost-effectiveness of alcohol control policies: an English perspective. *Lancet* 2017; 389: 1558–80	2017	NR	8	1	2	NA	1	2	2
81	Goh, E.T. & Morgan, M.Y. Review article: pharmacotherapy for alcohol dependence – the why, the what and the wherefore. *Aliment Pharmacol Ther* 2017; Apr; 45(7): 865–882.	2017	NR	6	2	1	11	3	2	2
82	Stockings, E. & Farrell, M. Drinking reduction goals offer potential to widen the options for measuring and treating alcohol dependence. *The Lancet Psychiatry* Vol 4 No 6 Pages 430-431.	2017	NR	7	3	2	9	4	2	2

83	Soyka, M. & Muller, C.A. Pharmacotherapy of alcoholism – an update on approved and off-label medications. *Expert Opinion on Pharmacotherapy* Vol 18 No 12 Pages 1187-1199.	2017	NR	6	5	3	12	6	1	2
84	Anderson et al. Managing alcohol problems in general practice in Europe: Results from the European ODHIN survey of general practitioners. *Alcohol and Alcoholism*, 49(5), 531-539.	2014	OS	10	1	2	9,10,11	1	1	2
85	Rahhali et al. Modelling the consequences of a reduction in alcohol consumption among patients with alcohol dependence based on real life observational data. *BMC Public Health* (2015) 15: 1271	2015	OS	7	4	NA	9	5	1	1
86	Bramness et al. Marketing status and perceived efficacy of drugs for supporting abstinence and reducing alcohol intake in alcohol use disorders: A survey among European Federation of Addiction Societies in Europe. *European Addiction Research* 2016;22:318–321	2016	OS	6	1	2	9,11	1	1	2
87	Manthey et al. Alcohol use disorders in Europe: A comparison of general population and primary care prevalence rates. *Journal of Substance Use* 2016; 21(5): 478-484.	2016	OS	11	4	NA	10	5	1	1
88	Barrio et al. Self-management and shared decision-making in alcohol dependence via a mobile app: a pilot study. *Int.J. Behav. Med.* 24, 722–727 (2017).	2017	OS	8	4	NA	9	5	1	1
89	Kraus et al. Alcohol screening and alcohol interventions among patients with hypertension in primary health care: an empirical survey of German general practitioners. *Addiction Research & Theory* 2017 Vol25, No4 285-292.	2017	OS	10	4	NA	10,11	5	1	1

90	Witkiewitz et al. Clinical Validation of Reduced Alcohol Consumption After Treatment for Alcohol Dependence Using the World Health Organization Risk Drinking Levels. *Alcohol Clin Exp Res*. 2017 Jan;41(1):179-186.	2017	OS	7	4	NA	9	5	1	1

1.'OT'=Original Trial paper; 'SA'=Secondary Analysis paper; SR/MA'=Systematic Review and/or Meta-Analysis (nalmefene efficacy); 'Other SR/MA'=Other Systematic Review and/or Meta-Analysis including nalmefene; 'Other N'=Other Study of Nalmefene; 'NR'=Narrative Review; 'OS'=Other study about alcohol treatment.
2. See coding framework: Chapter 6, Table 20.
3. COI and funding information was available in abstract obtained.
4. COI/Funding complex: Paper is an 'ADIS Drug Evaluation'. The author is affiliated to medical publishing company ADIS. No COIs are declared, but this author has reviewed other Lundbeck products; in addition, drafts were also reviewed by Lundbeck as well as individuals with Lundbeck COIs, including nalmefene trial authors.
5. Lundbeck COI not declared in paper but declared elsewhere (Owens et al., 2015; Luquiens et al., 2016)

Table 2: Description of grey literature documents

ID	Description of document/activity
R1	Report raising awareness of alcohol harms and calling for better strategies to address these. Focuses on investment in alcohol treatment. Lundbeck *"partnered*" with Alcohol Concern to produce the report, and provided funding and assistance from a medical writing company.
R2	Report on alcohol misuse and services in Wales, calling for more investment in treatment. Lundbeck "*part-funded*" its production.
R3	Report raising awareness of alcohol harms and interventions to reduce these, and to guide the implementation of the government's alcohol strategy. Focuses on individual level approaches. The Foreword is written by an MP. Produced by the British Liver Trust *"in partnership*" with Lundbeck, who provided an educational grant (report development, medical writer, and editorial and administrative support).
R4	An "*Advanced Planning"* document from Lundbeck to NHS managers prior to UK authorisation of nalmefene. Advance information about nalmefene and when it will be launched in the UK, promotes reduced drinking, highlights limited availability of treatment options and describes the nalmefene RCTs as demonstrating efficacy.
R5	Report on screening and brief interventions in chronic disease groups in primary care. Project was managed by Alcohol Concern, and funded by Lundbeck. Alcohol Concern and NHS Wandsworth were involved in the project.
R6	Booklet to help healthcare professionals identify appropriate treatment goals for different alcohol dependent patients. Lundbeck convened an expert group to develop the booklet, and paid for honoraria, expenses and outputs from discussions.
R7	Report calling for 15% of dependent drinkers to access treatment by 2015. Highlights reduced drinking approach in opening up access to treatment. Described as an "*independent*" report initiated and sponsored by Lundbeck, who also funded its production. Alcohol Concern and British Liver Trust were expert reviewers. Logos for Lundbeck, Alcohol Concern and British Liver Trust appear on the second page of the report.
R8	Online report supporting a reduced drinking approach to alcohol treatment. Lundbeck provided editorial support for the report, which was written by individuals on the Lundbeck-supported expert development group for the Integrated Care Pathway tool.
R9	Report based on an audit of the focus on alcohol-related harm in local authority planning documents. Highlights a lack of attention given to care pathways. Researched and written by Alcohol Concern. It also states that Lundbeck "*partnered*" with Alcohol Concern in producing the report, including assistance from a medical writing company.
R10	Report on alcohol harms in Northern Ireland and recommendations for addressing these through greater access to treatment. The Foreword was written by a Minister, and input and endorsements from two charities (Addiction NI and FASA) were acknowledged. Lundbeck initiated and sponsored the project (funding for writing, design, printing and administrative support through a public affairs company, which facilitated the production and launch of the report).
R11	Report of a project on implementation of NICE TA325 (nalmefene) across England to gain insight into implementation issues. The NIC are a partnership between the NHS, the life sciences industry, healthcare professional bodies, and health organisations, including NICE and the ABPI. Lundbeck contributed funding support for the project; most of the contributors to the report have Lundbeck COIs.
R12	Alcohol Concern factsheets to raise awareness of the links between alcohol and health conditions. Prepared with Lundbeck funding.
R13	Report asks political parties to commit to a wide range of measures to reduce alcohol harm (pricing and marketing measures as well as measures to increase investment and access to treatment). Researched by Alcohol Concern in their APPG Secretariat role. Secretariat and printing costs of the report were supported financially by Lundbeck.
E1	Lundbeck provided an unrestricted educational grant to fund this alcohol conference/CPD event for clinicians. (Medical Council on Alcohol, 2012). Also online: https://www.m-c-a.org.uk/events/2012_del_prog

E2	Meeting on "Alcohol Dependence - in Scotland" at the Scottish Parliament (discussed in the minutes of the Scottish Cross Party Group on Drugs and Alcohol, 2013). Organised and sponsored by a charity the Wellbeing Alliance; Lundbeck also sponsored the event (Powerbase, 2013). Screenshot of the invite can be accessed online: https://powerbase.info/index.php/File:Jackie_Baillie_invite_to_Parliament-Lundbeck-Wellbeing_Alliance-Screenshot_2013-10-31_13.26.15.png Questions about the Wellbeing Alliance, their work with Scottish Parliament committees and possible relationship with pharmaceutical companies, including Lundbeck, were raised at the time by others.[1] [2]
E3	Lundbeck funded conference venue costs (Alcohol Concern, 2014a). A session on "*Working with CCGs on Alcohol: Integrated Care Pathways in Kent*" (this care pathway was developed with funding by Lundbeck) was included. An online flier can be viewed at: https://www.eventbrite.co.uk/e/alcohol-concerns-annual-conference-2014-registration-10539196019#
E4	Lundbeck funded conference venue costs (Alcohol Concern, 2015e): https://web.archive.org/web/20150906135445/http://www.alcoholconcern.org.uk/training/events-for-professionals/
E5	CPD event for primary care nurses, which included a Lundbeck-sponsored workshop with sessions on: "*An overlooked comorbidity? Recognising and addressing the alcohol dependent patients already in your waiting room*" and "*Reviewing the pharmacological options for managing alcohol dependence in primary care*" (PDF of flier available on request)
E6	Lundbeck-funded educational event for GPs and mental health professionals. Presents evidence on the effectiveness of online video brief advice for alcohol and how it can be implemented in general practice (HAGA, 2015). See flier at: http://www.haga.co.uk/wp-content/uploads/2015/05/HAGA_Head_in_the_Cloud_Flyer_28.5.15.pdf
E7	Lundbeck part-funded this conference of the charity CRI. One presentation was organised and funded by Lundbeck: *"An alternative pharmacological approach in helping certain alcohol dependent patients to reduce their alcohol consumption"* (CRI and the University of Manchester, 2015). See flier at: https://web.archive.org/web/20150506041152/www.cri.org.uk/clinical
E8	A UK-based multidisciplinary group of alcohol experts convened by Lundbeck to discuss the management of alcohol dependence.
E9	A Lundbeck-sponsored and organised meeting for GPs in Scotland. Sessions on primary care management of alcohol dependence, treatment goals, and the use of nalmefene (Gordon, no date) Available online at: https://www.pinterest.co.uk/peterjgordon/pharmaceutical-sponsored-medical-education/
E10	A Lundbeck-organised expert meeting, aiming to address alcohol misuse and related health conditions including hypertension. Attended by alcohol experts, alcohol charities, Lundbeck staff and staff from a medical communications company (Lundbeck Ltd., 2014d). PDF available on request.
E11	APPG on Alcohol Misuse discusses alcohol related issues, and makes recommendations to government and other policy makers. Lundbeck provided funding to Alcohol Concern to run the APPG Secretariat (UK Parliament, 2014). Funding also provided for the production of the APPG's Manifesto Report (see R13).
E12	Regional network meetings were supported by an unrestricted educational grant from Lundbeck. One agenda item was: "*Applying NICE in Alcohol Pathways - a case study*" (delivered by a GP who has worked with LB). (West Midlands Mental Health Commissioning Network, 2015) At another meeting Kent County Council presented on their Lundbeck-supported ICPs project and how to use data from the Lundbeck-supported Alcohol Impact Model (Kent County Council, 2014a). Available at: (SEMHCN October 14th 2014 - Alcohol Harm Reduction Pathway in East Kent)
P1	Lundbeck funded Alcohol Concern to develop an online tool for local statistics on alcohol harms and costs. Funding covered project management support from a communications consultancy, design and development of the map and collation of data.
P2	Lundbeck funded a modelling tool to help identify the impact of alcohol misuse at a local level. This featured in Lundbeck presentations to Regional NHS Networks Groups (NHS Networks, no date) and in the Kent ICP (Kent County Council, 2014b)
P3	Lundbeck funded projects on developing patient care pathways for alcohol. These involved joint working with Kent County Council Public Health Team (Lundbeck Ltd., 2014c), East Surrey CCG (Lundbeck Ltd., 2014b) and Wessex Academic Health Sciences Network (WAHSN) (Lundbeck Ltd., 2014a).

	Details of the South Kent Coast and Thanet locality pathway are available in its specification document (Kent County Council, 2014b). The remit of the joint work with WAHSN was to evaluate a treatment pathway for patients with increasing and higher risk drinking levels, which included creating "*more opportunities for the appropriate use of medicines, including not exclusively, nalmefene*" (Lundbeck Ltd., 2014a). Lundbeck also funded the development of an online interactive tool for commissioners to develop alcohol ICPs in their areas. This involved a diverse group of alcohol experts (charity, commissioning, service provider, patient expert, clinical and pharmacy). The online tool references the Lundbeck-supported Alcohol Harm Map and Alcohol Impact Model as data sources to identify local need (Integrated Care Pathways Development Group, 2015).
S1	Submission of evidence from Lundbeck to a national committee considering alcohol misuse and policies in Wales.
S2	Submission of evidence from Lundbeck to a consultation on alcohol and drug commissioning for Northern Ireland.

1. Letter from Professor David Miller to the Scottish Parliament Standards, Procedures and Public appointments Committee (published on the Scottish Parliament website). It raises issues of 'lobbying' at the Scottish Parliament and the role of the Wellbeing Alliance. He notes that the Wellbeing Alliance provided secretarial support to various cross-party groups and sponsored a meeting in Parliament 'Alcohol dependence – in Scotland' (also sponsored by Lundbeck). He calls for the Committee to ask for details about the nature of the relationship between the Cross Party Groups, Wellbeing Alliance and Lundbeck. (Miller, 2014).
2. Powerbase web page about the Wellbeing Alliance, covering their role and links with pharmaceutical companies (Powerbase, 2014)

Appendix 4: Qualitative fieldwork documents

UNIVERSITY of STIRLING

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PARTICIPANT INFORMATION SHEET

Nalmefene for alcohol dependence: Qualitative interview on how nalmefene has been viewed, used and promoted in the UK

You are invited to participate in a brief telephone interview about nalmefene. This will cover your role and experience of nalmefene; your views about nalmefene and its licensing conditions; your experience of prescribing and insights in relation to UK prescribing levels; and your experience and views about activities relating to nalmefene promotion.

This work contributes to a PhD which is being undertaken at Stirling University. The PhD student and lead researcher is Clare Sharp, and the academic supervisors are Dr Niamh Fitzgerald and Professor Linda Bauld. The study is funded by Alcohol Change UK and Stirling University.

This sheet outlines the study background and what is involved for participants. If you would like to discuss the study, please get in touch using the contact details at the end of this sheet.

Background

Nalmefene is a drug which was approved for use in the UK in 2013 to treat alcohol dependence. It is the only drug licensed for the reduction of alcohol consumption; other alcohol dependence drugs are licensed for maintaining abstinence in individuals who have stopped drinking. It is authorised for use in a specific group of people – those with alcohol dependence, without physical withdrawal symptoms, who have a high drinking risk level at both initial assessment and two weeks later, and who will also receive continuing psychosocial support to help them take their medication. Qualitative interviews with a range of professionals from the alcohol treatment field will be used to explore their views of nalmefene and its role in alcohol treatment. The results from these interviews will complement earlier work conducted for this mixed methods study, which has involved an analysis of promotional activities relating to nalmefene and an analysis of GP prescribing data to understand how nalmefene has been used in primary care.

Why have I been invited to take part?

This study aims to seek the views of a range of professionals who have some expertise or knowledge in the field of alcohol treatment and services, and in particular, those who may have experience or knowledge of nalmefene use or promotional activities. Potential

participants have been identified via key contacts made during the scoping work for this study as well as through publically available literature relating to nalmefene.

Do I have to take part?

Taking part is voluntary. If you do decide to take part, you can withdraw your participation at any time without giving a reason.

What is involved?

You are asked to participate in a brief telephone interview (of approximately 45 minutes). If you are happy to take part, please complete and sign the enclosed Consent Form. Electronic signatures can be used if you wish to reply by email or, if you prefer, you can return a hard copy using a reply paid envelope (to be supplied on request). The lead researcher will contact you to arrange a suitable time for the interview. With your permission, the telephone interview will be audio-recorded and transcribed.

Are there any potential risks in taking part?

No potential risks from taking part are anticipated. Care will be taken to ensure that all data gathered is anonymised in order to protect the identity of participants.

Are there any benefits in taking part?

Taking part in the study may not offer any direct benefit. However, your contribution will help to provide a more complete picture of nalmefene use in the UK, which in turn will inform the wider debate around alcohol treatment and regulatory processes.

What happens to the data I provide?

The interview will be recorded (with your permission), and the audio recording downloaded to a secure folder on a University of Stirling computer, which is password protected. Once transferred, the audio file will then be deleted from the recorder. The recordings will be transcribed, and transcriptions saved in a secure folder on a University of Stirling computer, accessed only by the lead researcher and her supervisors. The transcripts and any data obtained from them will be anonymised. Any names or identifying information will be removed and replaced with a participant code. The data generated will be used in the thesis and any resulting reports, conference papers or publications. Participants will have the opportunity to review their interview transcript once it is available.

Your consent for the use of the anonymised data, including quotes if appropriate, will be sought (please complete the attached Consent Form). For more information on how any personal data is managed and your rights under the General Data Protection Regulations, the University of Stirling Data Protection Policy can be accessed online at:

https://www.stir.ac.uk/media/stirling/services/policy-and-planning/gdpr/documents/GDPRPolicy.pdf

Who has reviewed this research project?

This project has been ethically approved via The University of Stirling NHS, Invasive or Clinical Research Committee.

Contact for further information

You can contact the lead researcher Clare Sharp (clare.sharp1@stir.ac.uk; phone 07719 368743) or her academic supervisors Dr Niamh Fitzgerald (Niamh.Fitzgerald@stir.ac.uk; phone 01786 467362) and Professor Linda Bauld (Linda.Bauld@ed.ac.uk; phone 0131 650 3213).

Contact for concern or further comments

If you have a concern or any comments and would like to speak to someone who is not directly involved in the study, please contact Professor Jayne Donaldson, University of Stirling (jayne.donaldson@stir.ac.uk; phone 01786 466345).

Thank you for taking the time to read this participation sheet.

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CONSENT FORM

Nalmefene for alcohol dependence: Qualitative interview to understand how nalmefene has been viewed, used and promoted in the UK

Please place your **initials** in the boxes alongside each statement and **print** and **sign** your name to indicate that you consent to take part in the study above.

1. I confirm that I have read and understood the Participant Information Sheet. ☐
2. I have had the opportunity to discuss the study and ask questions. Any questions I had have been answered to my satisfaction. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any point up to when the study is published. ☐
4. I agree to participate in the research. ☐
5. I agreed to the discussion being audio-recorded and transcribed, and for data from the transcripts to be used in research publications or reports, with strict preservation of anonymity (please tick box) ☐ ☐

Please complete and sign this consent form. You can complete this electronically by inserting an electronic signature and emailing the form to: clare.sharp1@stir.ac.uk. (If you would rather sign and return a paper copy by post, a reply paid envelope will be available to you on request.)

Name of Participant (please print)	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature
_____	_____	_____

Thank you for taking part in this study

Topic Guide outline

Your role

1. Can you tell me briefly about your role and how this relates to alcohol?
(Prompt: Setting, whether sees patient and type of patients, type of treatments offered)

Knowledge of nalmefene

2. Can you tell me what you know about nalmefene?
(Prompt: familiarity with evidence, licensing conditions, the nalmefene patient group)

3. What sources of information have you been informed by?

Local delivery of nalmefene

4. How is nalmefene made available locally to prescribe (if it is available)?
(Prompt: who can prescribe it (GPs v specialist services), is there a pathway/process for nalmefene e.g. a shared care agreement)

5. How well do you think this process works?

6. [If not available locally] Why is nalmefene not available in the local area?

Views on the value of nalmefene and its licensing conditions

7. What are your views on the value of nalmefene in general to alcohol treatment?

8. Why do you say that?
(Prompt: role of the evidence, views about the licensing conditions)

9. What are your views on the nalmefene licensing conditions
(Prompt: how these work in practice, prescribing within these, prescribing outwith these and views about this)

Own prescribing

10. Have you prescribed nalmefene for any patients?

11. [If yes] Can you talk me through how you prescribed the drug?
(Prompt: key decisions, adherence to licensing conditions including psychosocial support *provided, number of prescriptions – did they receive more than one?)*

12. [If yes] What kind of patients did you prescribe to?
(Prompt: type of drinker, newly presenting or already received treatment, did patients know about nalmefene and how?)

Perceptions of nalmefene use more widely and factors influencing this

13. How widely do you think nalmefene is used in the UK or more locally?
(Prompt: why they say that)
(Prompt if needed: Issues relating to the evidence, the licensing conditions, setting for nalmefene, identifying patients, current service provision; views about treatment)

Experience of activities organised by Lundbeck (who manufacture nalmefene)

14. Do you have any experience of activities organised by Lundbeck?
(Prompt: attendance at events, work on projects, general awareness of activities)
(Prompt: what were they about, aims, key messages, who was there?)

15. What were your view of these?
(Prompt: usefulness, influence, and in what way)

Summing up

16. Do you have anything else to add about nalmefene or anything we have discussed?

Thank you

Appendix 5: Qualitative analysis framework matrix

Table 1: Final framework matrix headings and definitions

Categories and sub-categories	Definitions
1. Participant background	
1.1 Professional background and experience	1.1 Current role and previous roles relating to alcohol problems, and whether these have involved seeing patients
1.2 Experience of nalmefene	1.2 Level of knowledge about nalmefene, experience of prescribing, experience of working with Lundbeck on nalmefene
2. Perspectives on the value of nalmefene	
2.1 An additional tool	2.1 Valuable for clinicians to have another treatment option
2.2 Engaging with patients	2.2 Valuable in helping to engage with patients; the appeal of a harm reduction approach
2.3 Helpful for some patients	2.3 Patients who can benefit from nalmefene
2.4 Changing the narrative around alcohol problems and how to treat them	2.4 Widening the discussion to include alcohol problems as a spectrum; harm reduction approaches
2.5 Problems with the evidence	2.5 Weak evidence, industry-sponsored, conduct of the trials, lack of transferability, type of psychosocial support
2.6 Not a novel treatment	2.6 Similarity to naltrexone
2.7 Medicalisation	2.7 Disagreement that a pharmacological approach is right for this group of patients
3. Nalmefene implementation and uptake: perceived facilitators	
3.1 Patient power	3.1 Patient awareness of the drug; patient pressure on GPs
3.2 The media	3.2 Media coverage of nalmefene, positive stories, creating interest in patients, and putting pressure on authorities
3.3 NICE endorsement	3.3 Influence of NICE approval; added authority of the NICE Technology appraisal
3.4 Experts	3.4 Interest and enthusiasm from experts, influence of powerful academics
3.5 Something new	3.5 A new drug in an area which has not seen any new developments; generates interest
3.6 A pressure to act	3.6 Extent of alcohol problems; pressure to deal with these
3.7 Missed opportunities	3.7 Approaches which could have helped to establish nalmefene more widely: making it an adjunct to psychosocial support; GP incentives; an enhanced service; training; specialist clinics and other settings
4. Marketing and promotion of nalmefene	
4.1 Type of event	4.1 Description of the type(s) of event or activity (based on participant experience or awareness); participant involvement
4.2 Aim of event	4.2 Key content, messaging and aims
4.3 Impact	4.3 Impact of events or activities on implementing, and prescribing nalmefene
4.4 Risks and benefits	4.4 Views about the risks and benefits from these promotional events or activities
4.5 Getting involved in the nalmefene promotional events	4.5 Views about attending or getting involved in Lundbeck-sponsored work on nalmefene; wider views on working with pharma
4.6 Marketing approach for nalmefene	4.6 Perspectives on the overall approach; successes and failures
5. Prescribing experiences	
5.1 Prescribing experience	5.1 Level of participant experience of prescribing nalmefene; number of patients
5.2 Type of patient	5.2 Description of patients who have been prescribed nalmefene; level of alcohol problems; type of drinker; prior alcohol treatment; level of awareness of nalmefene; views

	about the licensed patient group
5.3 Patient experiences	5.3 Describes patient experiences of nalmefene; number of prescriptions; whether it was helpful; side effects
5.4 Delivery of nalmefene	5.4 Description of how nalmefene was delivered locally; place in formulary; setting; alcohol care pathways; provision of psychosocial support;
6. Nalmefene implementation and uptake: perceived barriers	
6.1 Current alcohol treatment system	6.1 Factors relating to how alcohol problems are dealt with in the current system – primary care role, specialist services role, funding, priorities
6.2 Beliefs about alcohol problems and treatment	6.2 Different opinions and beliefs about alcohol problems and how to treat them
6.3 The evidence	6.3 Factors relating to the evidence - lack of faith in RCTs evidence, awareness of negative journal articles
6.4 Licensing conditions for nalmefene	6.4 Factors relating to the licensing conditions – diagnosing alcohol dependence, providing psychosocial support
6.5 Attitudes to alcohol	6.5 Attitudes which make it challenging to reach the nalmefene patient group, patient attitudes, clinician attitudes, normalisation of drinking