Opioids for musculoskeletal pain and their associations with reproductive and sexual function in women: an epidemiological study

Emily Richardson

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Keele University

Arthritis Research UK Primary Care Centre

Research Institute for Primary Care & Health Sciences

Declaration

This thesis was undertaken as part of a School for Primary Care Research Academic Clinical Fellowship and a National Institute for Health Research In-Practice Fellowship. The views expressed are those of the author and not necessarily those of the NIHR or Department of Health and Social Care. The idea for the CPRD cohort study arose from Kate M Dunn and the research proposal was written by John Bedson, Kate M Dunn and Ying Chen and ethical approval was gained. The idea for the cross-sectional study was developed initially by myself with input from John Bedson, Kate M Dunn and Ying Chen and I led the proposal development and ethical approval process.

I was responsible for the development of Read Code lists for outcomes and possible confounders for CPRD and these were used by Ying Chen to develop the database for the CPRD cohort study. I undertook analysis with statistical support from Ying Chen.

I was responsible for the design of the cross-sectional study, data collection (in collaboration with the West Midlands Clinical Research Network), data entry and data analysis. Ying Chen provided support for statistical analysis.

The interpretation of the findings and discussion of these are my own.

Abstract

Background

One fifth of primary care attendees report chronic non-cancer pain (CNCP) most of which is related to musculoskeletal conditions, 12% of these are prescribed strong opioid analgesics. Evidence suggests long-term opioid use causes hypogonadism in men (including sexual reproductive dysfunction), but in women, the relationship is not known.

Aim

To investigate the relationship between opioid use and reproductive and sexual dysfunction in women aged 18-55 years old.

Methods

A systematic review summarised existing evidence for sexual and reproductive dysfunction in women prescribed opioids (>1 month) for CNCP. Two further original studies investigated women prescribed opioids for musculoskeletal pain. A clinical practice research datalink (a UK primary care database) cohort study compared the risk of four outcomes (irregular/absent menstrual cycles, menopausal symptoms, low libido and infertility) for long-term (≥3 months) and short-term opioid users. A cross-sectional study investigated the risk of female sexual dysfunction (FSD) dependent on daily oral morphine equivalent dose (MED).

Results

The systematic review identified 12 small papers, mainly from secondary care. Opioid use was associated with irregular menstruation, decreased libido and decreased sex hormone levels. In the cohort study (n=44260) there was an increased risk of abnormal menstruation (Hazard ratio (HR) 1.13; 95% CI 1.05, 1.21) and menopause (HR 1.16; 95% CI 1.10, 1.23) in long-term opioid users when compared to short-term users, but no association with infertility or low libido. The cross-sectional survey (n=153) found FSD in 50% of those receiving ≥20mg MED daily, falling to 31.7% in those not currently using opioids (OR 2.29; 95% CI 0.94, 5.55).

Conclusion

This thesis highlights that there is an increased risk of menstrual disturbances and menopausal symptoms with opioids and these should be considered when opioids are prescribed for CNCP. These findings may help management decisions in CNCP when discussing treatment options with patients.

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Abbreviations

AMED	Allied and complementary medicine
ASEX	Arizona Sexuality Experience Scale
BMI	Body Mass Index
BNF	British National Formulary
BP	Blood Pressure
CALIBER	Clinical research using Linked Bespoke studies and Electronic health Records
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval
CINAHL	Cumulative index to nursing and allied health literature
CNCP	Chronic non cancer pain
COCP	Combined oral contraceptive pill
CONSORT	CONsortium to Study Opioid Risks and Trends
CPRD	Clinical Practice Research Datalink
CRD	Centre for reviews and dissemination
DHC	Dihydrocodeine
DHEAS	dehydroepiandrosterone
DSM	Diagnostic and Statistical Manual of Mental Disorder
EMBASE	Excerpta Medical Database
ER	Emily Richardson
FSD	Female sexual dysfunction
FSFI	Female Sexual Function Index
FSH	Follicular stimulating hormone

FT	Free testosterone
GCSE	General Certificate of Secondary Education
GnRH	Gonadotrophin releasing hormone
GP	General Practitioner/General Practice
HDAS	Healthcare databases advanced search
HES	Hospital Episode Statistics
HPG	Hypothalamic-pituitary-gonadal
HRQoL	Health Related Quality of Life
HRT	Hormone Replacement Therapy
HRT	Hormone Replacement Therapy
HSDD	Hypoactive sexual desire disorder
ICD	International Classification of Disease
IM	Intramuscular
IQR	Interquartile range
IV	Intravenous
JB	John Bedson
KD	Kate M Dunn
LB	Laurna Bullock
LH	Luteinising hormone
M/R	Modified release
MAR	Missing at random
MCAR	Missing completely at random
MCS	Mental component score
MHRA	Medications and Medical Devices Regulatory Agency

MNAR	Missing Not at Random
MRR	Medical records review
MSK	Musculoskeletal
MST	Morphine Sulphate
N	number
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHR	National Institute for Health Research
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OECD	Organisation for economic co-operation and development
ONS	Office of National Statistics
OPIAD	Opioids induced androgen deficiency
OR	Odds Ratio
P	Probability
PCOS	Polycystic ovary syndrome
PCS	Physical component score
PHQ-2	Patient health questionnaire 2
POF	Premature ovarian failure
POP	Progesterone only pill
PPIE	Patient and public involvement and engagement
PPV	Positive predictive value
PR	Prolonged release
PRL	Prolactin

PsychINFO	Psychology and allied fields
QoF	Quality Outcomes Framework
QoL	Quality of life
RA	Rheumatoid Arthritis
RCT	Randomised controlled trial
ROC AUC	Receiver operating characteristic area under the curve
RUG	Research user group
S/L	Sublingual
SD	Standard deviation
SEM	Standard Error of the Mean
SF-12	Short-form 12
SHBG	Sex hormone binding globulin
SMOG	Simple Measure of Gobbledygook
SR	Slow release
STAMP	Smartphone and Tablet Application for Medications and Pain
T/D	Transdermal
TAPS	The STarT MSK Trial
THIN	The Health Improvement Network
TOXLINE	Toxicology Data Network
TROUP	Trends and risks of Opioids Use for Pain
TT	Total testosterone
TVC	Time varying components
UK	United Kingdom
USA	United States of America

WHO	World Health Organisation
WM:CRN	West Midlands: Clinical Research Network
YC	Ying Chen
YLD	Years Lived with Disability

1 Introduction

This thesis focuses on the study of opioid use for chronic non cancer pain (CNCP) in women, and sexual and reproductive adverse effects of those opioids. This chapter will introduce the subject of interest, and discuss the rationale for the thesis. The aims and objectives of the thesis will then be presented and finally this chapter will provide an overview of the remaining chapters of the thesis.

CNCP can be defined as any painful condition lasting for three months or more and not associated with cancer (Chapman et al., 2010). CNCP affects women more commonly than men and has been shown to affect 22% of those attending primary care, with musculoskeletal conditions as the leading cause of CNCP (Breivik et al., 2006; Gureje et al., 1998). A previous self-report survey of the general population (aged 25 years and over) in Scotland found that 50.4% of those who completed the survey reported chronic pain, this survey found women were more likely to be affected than men (Odds Ratio (OR) 1.24, 95% confidence interval (CI 1.07,1.43) (Elliott et al., 1999). Most patients with CNCP are managed in primary care (70%) with only a proportion (23%) being referred to a pain specialist (Breivik et al 2006). Recommendations for treating CNCP include self-care, physiotherapy, psychological approaches, medicine, surgery and alternative medicines (Turk et al., 2011). Opioids are often recommended as second line therapy for CNCP, and 62-63% of UK patients with CNCP were prescribed an opioid in a survey of CNCP in Europe (Breivik et al., 2006; Cheung et al., 2014; Chou et al., 2009b; Gureje et al., 1998; National Institute for Health and Care Excellence, 2014a). Opioids are analgesics used for treatment of moderate to severe pain (BNF, 2018a). The use of opioids for CNCP has increased over the past two decades with one study finding a 38%

increase in the incidence of prescribed opioids between 2002 and 2009 (Bedson et al., 2016). The evidence to show that opioids are effective in CNCP is weak, and adverse effects are a growing concern, with up to 80% of those treated with opioids experiencing at least one adverse effect, such as constipation, itching, dependency or tolerance (Els et al., 2017a; Eriksen et al., 2006; Kissin, 2013; Noble et al., 2010; The British Pain Society, 2010). With the increasing numbers of patients receiving opioids, previous authors have noted that even with low rates of adverse effects, large numbers within the population can be affected (Campbell et al., 2010; Sullivan et al., 2008).

The focus of the thesis is sexual and reproductive dysfunction and the relationship with opioid use, which has been highlighted previously as an area requiring further research by the American and British pain societies (Chou et al., 2009a; The British Pain Society, 2010). Endocrine dysfunction (particularly sexual and reproductive dysfunction) associated with opioid use has recently become an area of concern, This is thought to be related to a disruption of either the hypothalamic-pituitary-gonadal (HPG) axis and/or the hypothalamic-pituitary-adrenal (HPA) axis, which can lead to symptoms such as erectile dysfunction in men and amenorrhoea (absent menstruation), female sexual dysfunction (FSD), infertility and depression in women. Previous research has found good evidence that men taking long-term opioids (either prescribed or illegal) are affected by sexual dysfunction often associated with low testosterone; the primary mechanism for this effect in men is thought to be through suppression of the HPG axis (Abs et al., 2000; Aloisi et al., 2009; Benyamin et al., 2008; Daniell, 2002; Katz and Mazer, 2009; Smith and Elliott, 2012). This adverse effect in men is also known as opioid induced androgen deficiency (OPIAD), and has

been shown to affect up to 92% of men treated with long-term opioids (Abs et al., 2000; Aloisi, 2003; Benyamin et al., 2008; Daniell, 2002; Katz and Mazer, 2009; Rubinstein et al., 2013; Smith and Elliott, 2012). OPIAD in men appears to be linked more closely to the use of long-acting opioids rather than morphine equivalent daily dose (all opioid doses can be converted into a morphine equivalent dose, which is discussed in section 2.3), with one study finding 53% of male opioid users were affected overall, compared with 74% who used long-acting preparations (Rubinstein et al., 2013). Sexual and reproductive dysfunction have not been investigated so thoroughly in women. However, previous work in women taking illegal opioids (for instance heroin) has shown that women can be affected by amenorrhoea, galactorrhoea (inappropriate production of milk) and infertility, although hormone levels were often still within normal limits (Afrasiabi et al., 1979; Ballantyne and Mao, 2003; Bawor et al., 2015; Brennan, 2013; Brook and Marshall, 2001; Brown and Zueldorff, 2007; Colameco and Coren, 2009; Katz and Mazer, 2009; Pelosi et al., 1974; Smith and Asch, 1987; Stoffer, 1968; Williams et al., 2013). Symptoms of sexual and reproductive dysfunction, appear to improve when opioid dependency is treated with regular maintenance therapy (methadone and buprenorphine), and this relationship does appear to be dose related (Brown and Zueldorff, 2007; Schmittner et al., 2005). There is little published evidence relating to sexual and reproductive dysfunction when opioids are used legally to treat CNCP in women.

1.1 Thesis rationale

This thesis focuses on the use of opioids for women with CNCP in primary care, and sexual and reproductive dysfunction. Opioid use is increasing for CNCP, and the

majority of patients are treated in primary care (including ongoing prescribing of opioids if these have been recommended by secondary care), it is therefore important that this research is undertaken in primary care (Breivik et al., 2006). There has been limited previous research on sexual and reproductive dysfunction in women receiving legal opioids for CNCP. However, as discussed previously, there is evidence for sexual dysfunction in men receiving prescribed opioids, and also in women taking illegal opioids (Abs et al., 2000; Afrasiabi et al., 1979; Bawor et al., 2015; Brennan, 2013; Brown and Zueldorff, 2007; Daniell, 2002; Katz and Mazer, 2009; Pelosi et al., 1974; Rubinstein et al., 2013; Smith and Elliott, 2012; Stoffer, 1968). CNCP represents a significant burden on the NHS, and opioids are prescribed in a large proportion of these patients (Belsey, 2002; Breivik et al., 2006). Given the evidence of the relationship between opioid use and reproductive and sexual dysfunction in males using either illegal or prescribed opioids and in women receiving illegal opioids, it is reasonable to investigate this further in women receiving prescribed opioids for CNCP. It is important to determine if potential adverse effects exist because there would therefore be a need to discuss these with women prior to commencing opioids, and during any review of long-term opioid use. Given the above evidence, there is a strong case for investigating this further in women receiving opioids for CNCP in primary care.

1.2 Thesis aims and objectives

The overall aim of this thesis is to investigate the relationship between opioid use and reproductive and sexual dysfunction in women aged 18-55 years old.

The specific objectives are as follows:

1. To conduct a systematic review of the literature to identify and summarise the currently available evidence for reproductive and sexual dysfunction in women aged 18-55 years old receiving opioids for CNCP.
2. To investigate the relationship between opioid use for musculoskeletal pain and reproductive dysfunction. Reproductive dysfunction is defined based on symptoms and includes abnormal menstruation to less frequent or absent menstruation, menopausal symptoms/menopause and infertility.
3. To investigate the relationship between opioid use for musculoskeletal pain and female sexual dysfunction (FSD).

1.3 Outline of subsequent chapters

- **Chapter 2 background** information relating to the thesis. This chapter includes the definitions and epidemiology of pain. A definition of opioids and their pharmacology will be discussed, and the epidemiology of opioid use including effectiveness and adverse events are described. It also gives an overview of the endocrine system and a description of reproductive dysfunction that can occur. Finally the chapter explains FSD and the classification systems currently in use for diagnosing FSD.
- **Chapter 3 systematic review.** This chapter presents the findings of a systematic review of studies investigating sexual and reproductive dysfunction in women receiving long-term opioids for CNCP.
- **Chapter 4 methodology.** This chapter provides the background to the methods used within the remainder of the thesis and the underlying epidemiological concepts.

- **Chapter 5 cohort study methods.** This chapter provides the methods for the cohort study undertaken as part of this thesis within the clinical practice research datalink (CPRD).
- **Chapter 6 cohort study results.** This chapter provides the results from the cohort study, including a description of the population and a comparison of risk for four outcomes (abnormal menstruation, menopause/menopausal symptoms, low libido and infertility) using Cox regression. The two comparison groups within this study are long-term opioid users (90 days or more of opioid use) and short-term opioid users.
- **Chapter 7 cohort study discussion.** This chapter discusses the cohort study, with a summary of the main findings, comparison with other studies, the strengths and limitations of the study, the meaning of the study and any unanswered questions.
- **Chapter 8 cross-sectional study methods.** This chapter provides the methods for the cross-sectional study undertaken for the thesis. This study was a postal survey and the chapter includes information about the construction of the questionnaire.
- **Chapter 9 cross-sectional study results.** This chapter presents the results of the cross-sectional study. It includes the demographics of the study population and the results of logistic regression comparing groups based on daily morphine equivalent dose for a single outcome (FSD).
- **Chapter 10 cross-sectional study discussion.** This chapter discusses the cross-sectional study including a summary of the findings, comparison with

other studies, the strengths and limitations of the study, the meaning of the study, generalisability and any unanswered questions.

- **Chapter 11 overall discussion.** This chapter summarises the main findings from the studies included with the thesis, the strengths and limitations of the thesis overall, the implications for future research and suggests potential future relevant areas of research. It provides a conclusion for the thesis.

1.4 Summary

Prior research has demonstrated that reproductive and sexual dysfunction are common in men receiving prescribed opioids and in women taking illegal opioids, but few studies have investigated this in women taking prescribed opioids. Identifying whether a relationship is present in women taking prescribed opioids is important as it will help to shape discussions around the risks and benefits associated with opioid use for CNCP. This thesis will investigate the association between opioid use for CNCP and reproductive and sexual dysfunction.

This chapter has presented the outline of the remainder of the thesis. The next chapter provides a more in depth explanation of the core concepts important for the thesis including pain, opioids and the HPG axis.

2 Background

2.1 Introduction

Opioid use is recommended in guidelines for treatment of patients with chronic non cancer pain (CNCP) (Cheung et al., 2014; Chou et al., 2009a). However, evidence for the effectiveness of opioids in CNCP is poor (Noble et al., 2010), and adverse effects are common, affecting up to 80% of those receiving them (The British Pain Society, 2010). Recently, concerns have been raised around possible endocrine adverse effects from opioids and this thesis aims to investigate this area more fully, specifically investigating reproductive and sexual function in women.

2.2 Pain

Pain is defined by the International Association for the Study of Pain (IASP) as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”, and chronic pain as pain that continues after the normal time of healing (defined as three to six months) (Merskey & Bogduk 1994: p210). CNCP can be defined as any painful condition lasting for greater than or equal to three months and not associated with neoplastic disease (cancer) (Chapman et al., 2010). The most commonly reported cause for CNCP in a European study was arthritis/osteoarthritis (34% of respondents) and the most common location for CNCP was the lower back (24% of respondents) (Breivik et al., 2006). CNCP causes not just physical suffering but also associated disability and socioeconomic losses (through loss of working days), both for the person suffering and for society as a whole (Rhodin et al., 2010). The economic cost can be split into direct health care related costs (e.g. medicine costs, cost of appointments with

healthcare professionals) and indirect costs (e.g. loss of work days and productivity and benefit payments). A study in 1998 looking at chronic back pain within the United Kingdom (UK) found the direct costs to be £1632 million per year and indirect costs of £10668 million per year (making the cost of the provision of health care for the condition seem small); one of the key contributors to indirect costs was lost days of work and production (116 million lost work days in 1994-1995 due to back pain) (Maniadakis and Gray, 2000). In a chronic pain survey in Europe, one in four people with chronic pain, reported that pain had negatively impacted on their ability to work, with a mean loss of 7.8 days of work in six months (Breivik et al., 2006).

2.2.1 Epidemiology of CNCP

CNCP affects many people across the globe. A World Health Organisation (WHO) 15 centre study (5447 participants) showed that 22% of those attending primary care suffered from persistent pain, and women were more commonly affected than men (Gureje et al., 1998). The global burden of disease study 2010 found that musculoskeletal conditions were the second largest contributor of years lived with disabilities (YLD's) across nearly all world regions (Vos et al., 2012). A European study showed that 19% of adult Europeans suffer from chronic pain of moderate to severe intensity, and of these 40% consider their pain relief to be inadequate. The majority (70%) of these patients were managed in primary care by general practitioners, with 23% being seen by a "pain specialist" during the course of their condition. This study also showed that, in the UK, the median duration of pain was 5.9 years, and 37% of sufferers were not happy with their pain control (Breivik et al., 2006). In 2002, a study showed that Primary care workload for CNCP in the UK accounted for 4.6 million General Practitioner (GP) appointments which is the

equivalent of 793 full time GP's and a cost of £69 million to the National Health Service (NHS) (Belsey, 2002).

2.2.2 Women and pain

Women are affected significantly more by pain syndromes when compared to men (migraine in a ratio of around 4 to 1, fibromyalgia in a ratio of 3:1 and Temporomandibular Joint Dysfunction in a ratio of around 2:1), have a lower threshold for pain, greater pain related distress and are more likely to seek treatment for their painful condition (Bailey, 2013; Craft, 2007; Leresche, 1997; Lipton and Bigal, 2005; Paller et al., 2009; Queiroz, 2013). The reasons that women experience more pain than men are multifactorial and include physiological, psychological and cultural factors. When considering the question of women and how they experience pain, it is important to remember that the biological differences between women and men (their sex based on genetic differences determined at conception) are not the same as the gender differences (created through social expectations, and their influence during a child's development) (Greenspan et al., 2007). Women would traditionally (in terms of their gender) be expected to report symptoms of their pain earlier than when compared with men (Bailey, 2013). Women are also more likely to experience catastrophising, an abnormal psychological response to pain characterised by rumination, magnification and helplessness related to the pain; catastrophising has been shown to mediate the difference between responses to chronic pain by men and women (Paller et al., 2009). A systematic review in 2009 showed greater pain sensitivity in women compared to men in most pain modalities. Women were more likely to report musculoskeletal pain than men and osteoarthritis pain has been shown to be of a greater intensity in women (Fillingim et al., 2009).

Women have also been shown to have a higher likelihood of being affected by CNCP compared with men, and this includes the majority of musculoskeletal conditions. Pain in women tends to be more widespread, of greater intensity and longer duration than in men (Breivik et al., 2006; Campbell et al., 2010; Gureje et al., 1998). Musculoskeletal pain syndromes have been found to be up to 10 times more likely in women than men, and women are also more likely than men to develop a pain related disability (Bailey, 2013; Craft, 2007; Jordan et al., 2010; Unruh, 1996). A further systematic review in 2014 found that there was increasing prevalence of CNCP conditions in women during reproductive years and also found that musculoskeletal pain was worse during periods of low oestrogen within each monthly cycle (Hassan, Muere and Einstein, 2014).

Several reviews have looked at the biological differences in pain between women and men (rather than differences due to gender) and looked at the role of gonadal hormones (hormones produced in the ovaries and testes such as oestrogen, progestogen and testosterone) in pain (Greenspan et al., 2007; Hassan et al., 2014; Paller et al., 2009). These reviews found that females and males differ greatly in their response to pain and discuss the reasons for this difference between the sexes. It is thought to be partly due to the influence of gonadal hormones (e.g. oestrogen and progesterone in women and testosterone in men) which are likely to play an important role in abnormal pain states. The actual mechanism that links ovarian hormones (particularly oestrogen) with pain is unknown, but oestrogen is known to play a key role at several points in the pain pathway; at the afferent (sensing) nerves where the pain signal may be altered, in the spinal cord and in the brain where oestrogen receptors are found in key areas for pain, and also have effects on

neurotransmitters such as serotonin and dopamine (Hassan et al., 2014). Craft (2007) found that oestrogen was a key moderator in adult pain, but that this was a complex relationship and depended on changes in oestrogen levels and the type and duration of pain, and oestrogen could both improve and worsen pain depending on the mechanism in action. For instance pain in osteoarthritis has been shown to improve in high oestrogen states (e.g. pregnancy and post-menopausal women on hormone replacement therapy), whereas pain in lupus and temporomandibular disorders appears to worsen in high oestrogen states (and they also appear to worsen during peaks of oestrogen during the monthly menstrual cycle). Finally fibromyalgia has been shown to worsen when oestrogen levels are low (during the menopause and during menstruation) (Aloisi and Bonifazi, 2006; Craft, 2007; Paller et al., 2009). The difference between pain syndromes and how oestrogen levels change these is not fully understood, but is thought to be related to the mechanisms involved in the pain syndrome itself and how oestrogen interacts with these (Aloisi and Bonifazi, 2006). The link between gonadal hormones and pain is also supported by the presence of chronic pain conditions such as migraine that can be linked to the female menstrual cycle (Hassan et al., 2014). For instance, 80% of women with migraines have been shown to have complete relief of symptoms when pregnant (a high oestrogen state), and CNCP conditions increase in prevalence during childbearing years between menarche and menopause. This again shows that this is a complex relationship and oestrogen levels do not directly correlate with pain level and are dependent on multiple other factors, including the underlying pain condition itself (Aloisi, 2003; Aloisi and Bonifazi, 2006; Craft, 2007; Hassan et al., 2014).

2.3 Opioids

The British National Formulary (BNF) states that “Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin” (BNF, 2018a). Opioids are amongst the oldest painkillers known to man. Morphine, one of the strongest opioids, was originally produced from opium an extract of the “opium poppy” (Minami and Satoh, 1995; Vuong et al., 2010). Opioid drugs bind to opioid receptors (found in the brain, spinal cord and peripheral tissues) to produce their analgesic effect, and comprise of natural opioids (such as morphine), and synthetic opiates (such as diamorphine). The term opioids can be used to refer to all opioid analgesics regardless of source (Freynhagen et al., 2013; Reddy et al., 2010; Vuong et al., 2010).

Several opioid receptors exist including mu(μ), delta (δ) and kappa (κ), which can be found in the brain, spinal cord and afferent neurons (sensory receptors in the peripheral nervous system that send signals to the central nervous system). Opioids, either physiological (endogenous opioids) or pharmacological (exogenous opioids), bind to opioid receptors in order to exert their effect (Freynhagen et al., 2013; Grady et al., 2002; Minami and Satoh, 1995; Vuong et al., 2010), which is mediated both centrally (within the brain) and peripherally (within the nerves and spinal cord) (Minami and Satoh, 1995; Satoh and Minami, 1995; Stannard et al., 2013; Vuong et al., 2010). The action of opioids is dependent on the opioid receptor they bind to, the location of this receptor and the type of cell involved. Presynaptic opioid receptors inhibit the release of neurotransmitters, and post-synaptically they decrease the excitability of the neurone. Both of these actions decrease the transmission of pain signals and therefore the sensation of pain (Stannard et al., 2013).

Opioids are traditionally separated into weak or strong opioids based on relative effectiveness when compared to morphine. For instance, 100mg of oral codeine is equivalent to 10mg of oral morphine (relative potency of 0.1). There is wide variation of conversion values for opioids to morphine equivalent doses in the literature, and these can alter based on the route of administration and metabolism of medicines (altered by liver and renal function), meaning the conversion may be different in different patients (BNF, 2018b; Pereira et al., 2001). Throughout the thesis conversion factors used by Von Korff et al (2008) will be employed (Von Korff et al., 2008). A model for categorising analgesics including opioids into six groups has been developed by UK primary care physicians; in this model, opioids are split into four different potency categories including weak, moderate, strong and very strong and this will be used to categorise opioids throughout the thesis see Figure 2-1 (Bedson et al., 2013).

Opioids can also be separated by duration of action into either immediate or modified release. Short acting/immediate release preparations release all active ingredients on administration, giving a rapid onset and short duration of pain relief; these types of opioids are useful during dose titration (Fallon et al., 2006). Modified release preparations are designed to release the active ingredient at a predetermined rate to maintain a constant drug level over a specific period of time, normally once (24 hour slow release) or twice per day (12 hours slow release) preparations (Excellence, 2012; Fallon et al., 2006). See Table 2-1 summarising some of the commonly used opioids and their different formulations, split by strength and mode of action (Grady et al., 2002; The British Pain Society, 2010). However, Buprenorphine is pharmacologically different to other opioids. Buprenorphine is a mixed opioid agonist-

antagonist, it binds strongly to opioid receptors and is not easily displaced, meaning other opioids either physiological or pharmacological will have more difficulty binding to receptors (Walsh and Eissenberg, 2003).

Table 2-1 Summary of opioids (BNF, 2018a; The British Pain Society, 2010)

	Opioid Name (generic)	**Short acting preparations (examples)**	**Long acting preparations (examples)**
STRONG	Buprenorphine	Temgesic (S/L)	BuTrans, Hapoctasin, Transtec (T/D)
	Diamorphine	Oral or IV diamorphine	
	Fentanyl	Abstral, Effentora,	Fentanyl (T/D)
	Hydromorphone	Palladone (oral)	Palladone SR (oral)
	Morphine	Morphine Solutions (oral)	MST continus
	Oxycodone	Oxycodone	Dolocodon PR
	Pentazocine	Pentazocine (oral)	
	Pethidine	Pethidine (oral, IM)	
	Tramadol	Tramadol, Zydol (oral)	Tramadol M/R
WEAK	Codeine Phosphate	Codeine Phosphate (oral)	
	Dihydrocodeine tartate	Dihydrocodone tartate	DHC continus
	Mepatazinol	Meptid (oral)	

Key: S/L sublingual, T/D transdermal, IV intravenous, SR slow release, PR prolonged release, M/R modified release, IM Intramuscular

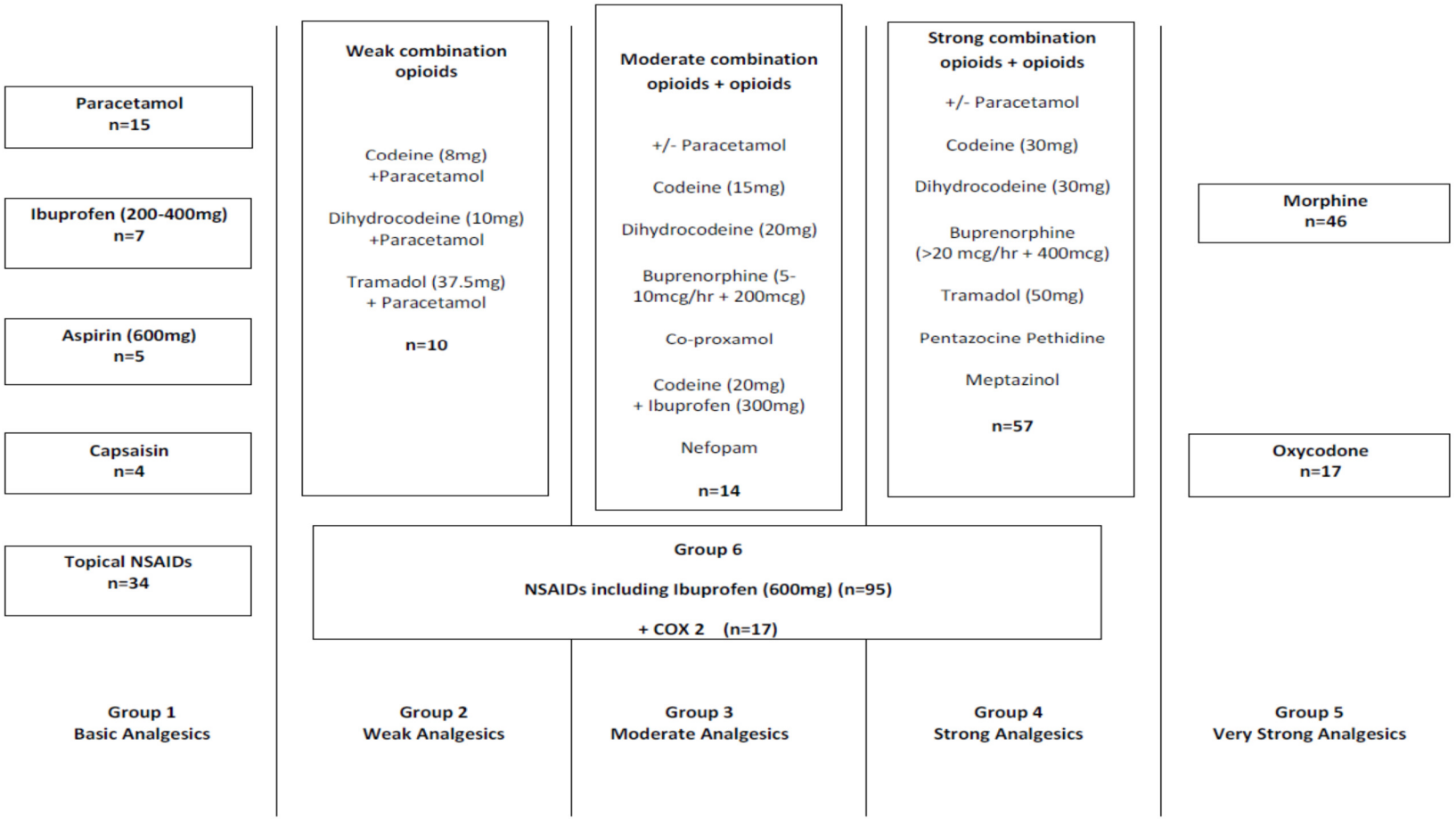


Figure 1– Analgesic categorisation for prescribing analgesics and NSAIDs in primary care where n = number of individual prescribable medication within that group

Figure 2-1 Analgesic categories reproduced from (Bedson et al., 2013). Key: NSAIDs non-steroidal anti-inflammatory drugs, COX2 cyclooxygenase-2, n number.

2.3.1 Opioids and effectiveness in CNCP

A Cochrane review on the use of long-term opioids (defined as > six months via oral, transdermal or intrathecal route) for CNCP in adults from 2010, identified 27 papers (open label case series and one controlled trial) (Noble et al., 2010). The authors of the review concluded that there was weak evidence for pain relief with oral opioids. The results were not generalisable to the whole population due to the lack of controls, and the studies being based around specific patient groups. The studies showed statistical heterogeneity, indicating variability between the studies combined for the meta-analysis. Heterogeneity can be reported using the I^2 statistic, and if the I^2 statistic is more than 50% it may represent significant heterogeneity, therefore the results of the meta-analysis may not be a true reflection of the actual effect (Higgins and Green, 2011). Studies of oral opioids showed a 63.4% mean decrease in pain score (Standard Mean Deviation 1.99, 95% CI 1.17, 2.8, I^2 = 51.3%), but there was a high dropout rate of study participants. 11.9% (95% CI, 7.8%, 17.7%) of subjects discontinued opioid use due to insufficient pain relief and 32.5% due to adverse events (95% CI 26.1%, 39.6%) (Noble et al., 2010). A further review in 2013 by a different author found no randomised controlled trial's (RCT's) that evaluated the long-term use of opioids (more than six months) and agreed with the Cochrane review that there was an absence of high quality evidence that might substantiate any recommendations in guidelines for the use of opioids (Kissin, 2013). A more recent trial in patients with low back pain and hip and knee osteoarthritis has found that opioid analgesics were no more effective than non-opioid analgesics for pain related function over 12 months of use, however the non-opioid analgesics group included tramadol on the third step of treatment, which in the definition of opioids used for this thesis would mean that opioid use was present in both comparison

groups (Krebs et al., 2018). In contrast, a systematic review in 2004 (18 RCT's follow-up was short ranging from four days to eight weeks with open label follow-up for up to two years) found a mean decrease in pain of 30%, but low dose opioids were ineffective and higher doses were of limited benefit due to adverse effects (Kalso et al., 2004). A recent Cochrane review that evaluated effectiveness of high dose opioids (>200mg morphine equivalent per day) found no evidence to support the use of opioids at this dose in CNCP (Els et al., 2017a). A review of guidelines developed for use of opioids in CNCP from 2004-2013 (seven national guidelines were identified), all discussed the limited evidence for long-term use of opioids, and recommended a discussion of risk and benefits prior to commencing opioids, and a trial of treatment to identify patient response and the dose required with tailored follow-up (Cheung et al., 2014). Despite the lack of evidence for use of opioids in CNCP, a postal survey of GP's showed that 83% (35% response rate) felt that opioids were effective for CNCP (McCracken et al., 2008). There is some evidence from a systematic review of open-label studies that some patients can benefit from long-term opioids, but opioids should only continue if there is clinically meaningful pain reduction, and if this is not evident a drug holiday should be considered (Hauser et al., 2015). Opioids continue to be recommended by experts as part of multi-disciplinary treatment of CNCP, patients should be monitored regularly and the dose should not be escalated above 120mg/day morphine equivalent dose without specialist input (O'Brien et al., 2017).

Several studies have found a relationship between treatment with opioids and poor patient outcomes. A population based cohort study set in Sweden found that rather than opioids being associated with improved pain scores, use of strong opioids was associated with poor health related quality of life (QoL) and were a risk factor for

mortality (Sjøgren et al., 2010). The authors commented that they could not be sure the opioids caused increased mortality and decreased QoL since the causes may well be multifactorial. Another cross-sectional study based in Denmark also showed that those with CNCP on opioids, when compared to those not taking an opioid failed to achieve similar functional status, QoL and pain control, but as a cross-sectional study and there is no way to establish causality in these relationships (Eriksen et al., 2006). Patients with back pain who were prescribed opioids early in their management, had worse self-reported disability at six month follow-up, even when confounders such as CNCP were adjusted for; findings were statistically significant but the actual increase in disability score was small and unlikely to be clinically important (Ashworth et al., 2013).

2.3.2 Trends in opioid use

In 2013 the NHS in England prescribed 21,710,300 items classified as an opioid in the BNF, at a cost of £13.35/item. This was an increase of 5.3% in the total number of items from 2012 (Prescribing and Primary Care team, 2012, 2013). Several studies in the UK have shown increases in opioid usage; Zin et al (2014) found an increase in women taking strong opioids (four specific opioids were included in the study morphine, oxycodone, buprenorphine and fentanyl) for non-cancer pain of 575.3% between 2000 and 2010 using data from the Clinical Practice Research Datalink (CPRD), Ruscitto et al (2015) found an 18 fold increase in strong opioid prescribing between 1995 and 2010 in a region of Scotland (Tayside), Foy et al (2016) found prescribing of strong opioids (e.g. diamorphine, morphine, oxycodone, fentanyl, and buprenorphine) increased by more than six times between 2005 and 2012 in Leeds and Bradford, and Bedson et al (2016) found a 38% increase in

incidence of prescribed opioids between 2002 and 2009 in a CPRD database study (Bedson et al., 2016; Foy et al., 2016; Ruscitto et al., 2015; Zin et al., 2014). This trend of increasing opioid use has also been seen in the United States (US) where two large studies, TROUP (trends and risks of opioid use for pain) and CONSORT (consortium to study opioid risks and trends), showed year on year increases in opioid prescribing (Von Korff et al., 2008; Sullivan et al., 2008). Denmark has also seen a 600% increase in opioid prescribing over the past 20 years (Eriksen et al., 2006). These increases are despite poor evidence for the effectiveness of opioid therapy, which was discussed in depth in section 2.3.1 (Els et al., 2017a; Kalso et al., 2004; Kissin, 2013; Noble et al., 2010). These increases reflect a trend of increased opioid prescribing for CNCP since the early 1980's, when there was a change in perceptions and attitudes towards use of opioids. Patient advocacy groups and professional health organisations began to promote effective pain control for patients with CNCP through the use of opioids if necessary. An important aspect of this was to moderate the fear surrounding their use, and consequently this led to drug companies marketing their opioids more aggressively (Freynhagen et al., 2013; Sjøgren et al., 2010). This change in perceptions is reflected in a postal survey of UK GP's in 2008; 83% of those surveyed reported believing that opioids were effective for CNCP, but there were concerns about adverse effects, monitoring of patients and addiction (McCracken et al., 2008). The acceptance of opioids into mainstream care was facilitated by the introduction of the WHO analgesic ladder for cancer pain in 1986, which has three steps. The first step involves the prescribing of non-opioids such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). Step two involves the addition of an opioid for mild to moderate pain if pain remained uncontrolled, and in step three opioids for moderate to severe pain are

recommended for pain that failed to respond to step one and two (World Health Organisation, 1990). The WHO analgesic ladder was initially proposed for cancer pain, but it is often now applied more generally for CNCP despite not being validated in this setting (British Medical Association, 2017). A review of seven national guidelines (including two from the US and one from the UK) showed that opioids were widely recommended as second line therapy for CNCP, as part of an individualised approach to care, in line with the WHO analgesic ladder (Cheung et al., 2014; Chou et al., 2009b). The National Institute for Clinical Excellence (NICE) recommends the use of codeine for pain relief as second line (following paracetamol with or without topical NSAIDs) for osteoarthritis, one of the commonest musculoskeletal conditions (National Institute for Health and Care Excellence, 2014a).

WHO uses opioid consumption as an indicator of progress in pain relief within each country (Zin et al., 2014). Epidemiological studies looking at opioid use in the US and The Netherlands indicate that predictors for opioid use include: female sex, older age, already receiving an NSAID, living alone, shorter education history, poor self-rated health and being unemployed (Eriksen et al., 2006; Parsells et al., 2008). A study within Scotland found that women when compared to men had a higher odds of receiving opioids, odds ratio 1.44 (95% CI 1.38, 1.50) and these odds increased with escalating polypharmacy (0-4 other medicines vs. 15 or more medicines odds ratio of 20.7 (95% CI 18.9, 22.6)) (Ruscitto et al., 2015).

2.3.3 Opioids and adverse events

An adverse event is defined by the Medicines and Healthcare products Regulatory Agency (MHRA): “An adverse drug reaction (ADR) is a response to a medicinal

product which is noxious and unintended." (MHRA, 2014). Up to 80% of patients taking opioids will experience at least one adverse event, so these should be discussed with patients prior to commencing treatment (The British Pain Society, 2010). A recent Cochrane review found the absolute event rate for any adverse event when taking medium to long-term opioids was 78% and 7.5% for serious adverse events (Els et al., 2017b).

Acute adverse effects of opioids include sedation, nausea, dizziness, itching, constipation (40-45% of patients) and pupillary constriction (The British Pain Society, 2010). Tolerance to the majority of these adverse effects occurs within a few days but itching and constipation often persist. Respiratory depression is also a problem with acute therapy, but does not tend to occur in those using opioids long-term unless there is a major dose, formulation, or route of administration change (Baldini et al., 2012; Grady et al., 2002; The British Pain Society, 2010). A systematic review showed specific adverse effects such as constipation, somnolence, nausea, vomiting, dizziness and itching were significantly more likely to occur in those receiving oral opioids when compared to placebo (Kalso et al., 2004).

Chronic adverse effects include persisting acute adverse effects, but also dependency, tolerance, addiction, endocrine adverse effects (e.g. opioid induced endocrinopathy leading to sexual and reproductive dysfunction for which the evidence is unclear and is the focus of this thesis), immunological effects (some opioids have direct immunosuppressive effects, this area is little studied and the clinical impact of this is unclear), sleep disordered breathing and opioid induced hyperalgesia (Baldini et al., 2012; Grady et al., 2002; The British Pain Society, 2010). Tolerance is a loss of analgesic potency with the patient requiring ever increasing doses due to decreasing efficacy over time. This is not to be confused with opioid

induced hyperalgesia which is worsening sensitivity to pain due to increasing doses of opioids (Manchikanti et al., 2010). Some opioids for instance tramadol and methadone have also been shown to increase the risk of serotonin syndrome when used in combination with other serotonin releasing agents (e.g. antidepressants) (Rastogi et al., 2011). Opioids have also been shown to increase morbidity and mortality of those taking them. Adults over 60 years old taking long-term opioids at a dose of more than 50mg/day have a twofold increased risk of fracture, and patients taking high dose opioids (more than 100mg/day) are also at higher risk of overdose (Bedson et al., 2019a; Dunn et al., 2010; Saunders et al., 2009). All-cause mortality has also been shown to be higher in opioid users when compared to non-opioid analgesic use (anticonvulsants and low-dose tricyclic antidepressants) with a hazard ratio of 1.64 (95% CI 1.26, 2.12) within the first 180 days of therapy and this was even higher in the first 30 days with a hazard ratio of 4.16 (95% CI 2.27, 7.63) (Ray et al., 2016).

Authors of the CONSORT study in the US, which investigated opioid prescribing trends from 1997 to 2005, highlighted that even with low rates of adverse effects, there could potentially be a large effect on morbidity and mortality in the population due to the high rates of opioid use (Campbell et al., 2010; Sullivan et al., 2008). It is important to note that the reported rate of adverse effects from opioids is up to 80%, and in many trials there is a high drop-out rate secondary to these adverse effects (Kalso et al., 2004; Noble et al., 2008, 2010; The British Pain Society, 2010). A systematic review in 2004 of 14 randomised control trials (follow-up of up to eight weeks and then open label follow-up for up to two years in eight studies) found that with opioid treatment, compared to placebo, the number needed to harm was 4.2 (CI 3.1-6.4). This means that for every four people treated with opioids, one experienced

an adverse event that they wouldn't have experienced if treated with a placebo (Kalso et al., 2004). A systematic review found a discontinuation rate in those taking oral opioids due to adverse effects of 22.9% (95% CI 15.3, 32.8%), but there was a high level of heterogeneity in the group (I^2 = 95.8%) so the results should be interpreted cautiously (Noble et al., 2010).

In summary, opioids are associated with high rates of adverse effects ranging from simple problems such as constipation to much more serious consequences such as increased fracture rate, risk of overdose particularly in older patients, and increased mortality.

2.4 The endocrine system

The endocrine system consists of blood borne chemical messengers called hormones released from endocrine tissues, which circulate throughout the body and influence target tissues where they have a regulatory effect. The effects of the endocrine system are wide ranging and help co-ordinate the body's internal physiology including controlling growth, development, metabolism, thyroid functions and reproductive functions. The release of hormones within the endocrine system is most often controlled by a process of negative feedback, where a signal causes a response which then acts to reduce the amount of signal being sent, (Figure 2-2) and occasionally will have positive feedback loops (e.g. during childbirth and breast feeding) (Brook and Marshall, 2001; Pocock et al., 2013). Central to the endocrine system is the hypothalamic-pituitary axis. The hypothalamus is located in the brain and has complex neural inputs from virtually all areas of the brain and is regulated by higher centres within the brain, but also has autonomy in release of hormones, which enter the pituitary blood supply and exert an action on the pituitary's cells stimulating

them to produce and release further appropriate hormones. The pituitary is made up of the anterior and the posterior pituitary and is connected to the brain by the pituitary stalk, through which the connecting blood supply runs. These hormones released from the pituitary then act on a target organ, which in turn itself will release a hormone which has a physiological purpose and will affect the release of further hormones from the pituitary (direct feedback) and the hypothalamus (indirect feedback) (Figure 2-2) (Brook and Marshall, 2001).

The area of hormonal regulation that this thesis will focus on is that of female sex steroid production. This is mainly via the hypothalamic-pituitary-gonadal (HPG) axis, with particular interest in the ovaries. The hypothalamus releases gonadotrophin releasing hormone (GnRH) which acts on the pituitary, where luteinising hormone (LH) and follicle stimulating hormone (FSH) are secreted from gonadotrophs (10-15% of cells in the anterior pituitary). These exert an action on the ovaries causing the release of gonadal hormones including oestrodiol, progesterone and inhibin (Figure 2-3), which support normal sexual and reproductive behaviour (Table 2-2) (Brook and Marshall, 2001; Katz and Mazer, 2009; Pocock et al., 2013).

Table 2-2 Summary of action of LH and FSH in women

Hormone	Affect in Women
Luteinising hormone	Induce ovulation Maintain secretory function of corpus luteum (a hormone secreting structure formed from the ovum (egg) following ovulation that disappears if fertilization does not occur) and therefore production of progesterone.
Follicle stimulating hormone	Stimulate development of ovarian follicles (the process during the first half of the month that surrounds the ovum with cells prior to ovulation) leading to secretion of oestrodiol Production of inhibin (prevents production of FSH by the pituitary)

Figure 2-2 Hypothalamic, pituitary, target organ axis. Adapted from Fig 3.3 Page 40 Essential Endocrinology 4th Edition (Brook and Marshall, 2001).

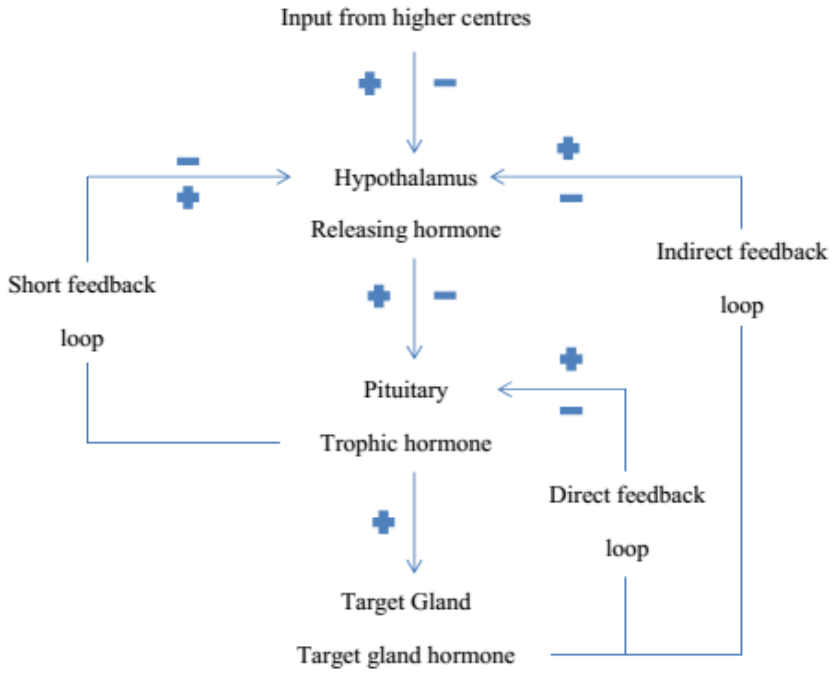
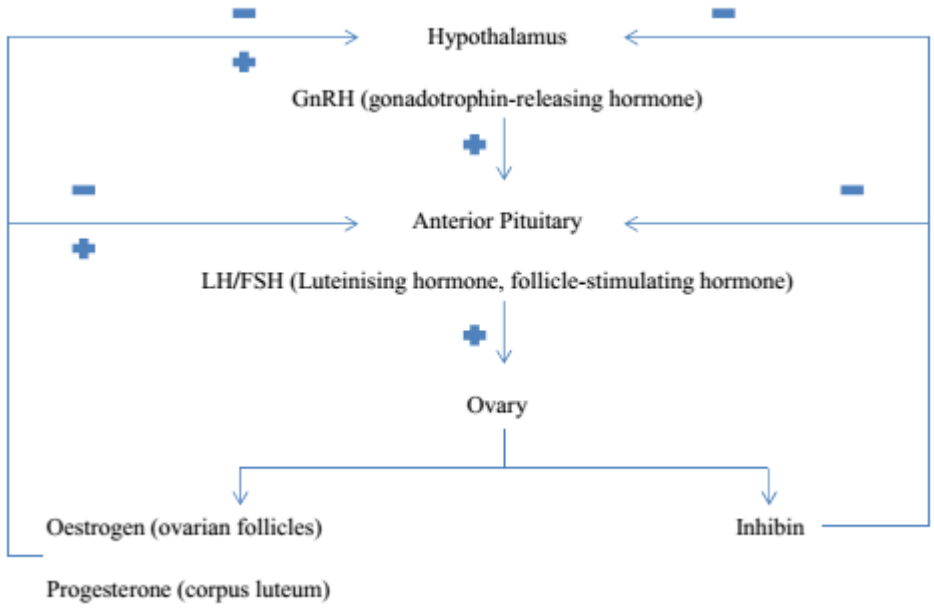


Figure 2-3 Hypothalamic, pituitary, gonadal (HPG) axis. Adapted from Fig 33.24 Page 677 Human Physiology 4th edition (Pocock et al., 2013).



2.4.1 Opioid induced endocrine adverse effects and their possible causes.

The possible endocrine implications of opioids in women are altered menstrual cycles, menopausal symptoms, female sexual dysfunction (FSD), infertility and possibly galactorrhoea as discussed in Chapter 1. Each of these has many potential causes and these will be discussed in the remainder of this section (Ballantyne and Mao, 2003; Brennan, 2013; Brown and Zueldorff, 2007; Colameco and Coren, 2009; Katz and Mazer, 2009; The British Pain Society, 2010). The mechanism for reproductive and sexual dysfunction is thought to be due to opioids creating a negative feedback effect on the hypothalamus, causing decreased GnRH release and subsequent decrease in gonadotrophin release, there may also be peripheral effects (see section 2.4 for more information on how the HPG system functions) (Smith and Elliott, 2012).

Amenorrhoea and oligomenorrhoea are associated with hypogonadism and are forms of menstrual cycle disorders. Amenorrhoea is a failure to menstruate; it may be primary (complete absence of menstruation) or secondary, which is defined as lack of menstruation for six months or more in a women or girl who has previously had normal menstruation (Brook and Marshall, 2001; Ojeda, 2011). Oligomenorrhoea can be defined as either an abnormally long period of time (35 days to six months) between regular menstruation, or less than nine menstrual cycles in a year (Impey and Child, 2012; Norwitz and Schorge, 2013; The Practice Committee of the American Society for Reproductive Medicine, 2008). The prevalence of amenorrhoea in the general population (not due to pregnancy, menopause or lactation) is between 3 and 4% (The Practice Committee of the American Society for Reproductive Medicine, 2008). The four main causes for secondary amenorrhoea are hypothalamic amenorrhoea, polycystic ovary syndrome (PCOS), hyperprolactinaemia and

premature ovarian failure (POF) (The Practice Committee of the American Society for Reproductive Medicine, 2008). There are however many more causes of amenorrhoea such as endocrine disorders (adrenal disease, thyroid disease including subclinical hypothyroidism and ovarian tumours), anatomical disorders and inflammatory/infective conditions can all cause irregular periods (Dickerson et al., 2009; Impey and Child, 2012; The Practice Committee of the American Society for Reproductive Medicine, 2008).

Hypothalamic amenorrhoea is due to an alteration in hypothalamic regulation of the HPG axis, due to a number of reasons including psychological stress, excessive exercise, nutritional changes and decreased weight which all lead to suppression of GnRH (The Practice Committee of the American Society for Reproductive Medicine, 2008). Hyperprolactinaemia can also cause amenorrhoea through suppression of GnRH production and is most commonly secondary to pituitary disease (usually benign) or prescribed medicines (Impey and Child, 2012; Melmed et al., 2011). PCOS affects around 5% of the population and accounts for nearly 80% of cases infertility due to anovulation (Impey and Child, 2012).

Alcohol intake can be related to the chances of achieving conception. One study found that Danish couples who consumed 10 or more alcoholic drinks per week were less likely to conceive a pregnancy than when compared with those drinking five or less drinks per week (Jensen et al., 1998). Smoking was found to be significantly associated in one study with premature ovarian failure (POF). (Chang et al., 2007; Luborsky et al., 2003).

2.5 Female sexual dysfunction

Female sexual dysfunction (FSD) covers a wide range of disorders with the common outcome that a person is unable to respond sexually or experience sexual pleasure (American Psychiatric Society, 2013). In women the normal stages of sexual function are arousal, the sexual act itself and orgasm (Bhugra and Colombini, 2013). Sexual function however is not purely a biological process it is complex and has personal, interpersonal and cultural influences (American Psychiatric Society, 2013). FSD can happen during any of the stages of normal sexual function, and a woman may be affected in more than one way. Sexual health is multidimensional, influenced and affected by the biological, psychological, medical conditions (including prescription medicines) and social factors including current relationship status. (Basson et al., 2001; Dalpiaz et al., 2008).

Corona et al (2006) state that “Sexuality is an integral part of being human, love, affection and sexual intimacy contribute to healthy relationships and a person’s happiness and self-esteem” (Corona et al., 2006). FSD affects a high proportion of women, but FSD is often ignored in health care settings. An example of this is a study by Read et al. (1997) where consecutive patients leaving a GP consultation were surveyed revealing that 42% of women attending in this primary care setting reported sexual dysfunction, a sexual problem was only coded in 2% of these patients’ notes (Read et al., 1997). A further study of older patients aged 40-80 years old, across 29 countries, found that 26-48% of women reported lack of interest in sex, but only 9% had been asked about sexual health during their routine health care visits in the previous three years (Laumann et al., 2005). A postal survey of the general population in 1998 (44% response rate) found that 41% of women reported a current sexual problem (median age 49 years old); in a subset of women 30-59 years

old the rate was 28% (Dunn, Croft et al. 1998). Improving sexual health has been shown to have an effect on quality of life overall. It is also important because sexual health problems can potentially be an early sign of other underlying systemic health conditions (Clegg et al., 2012). There are many barriers to discussion about sexual health and these come from both the clinician and the patient, for example limited time, embarrassment and the lack of treatment options (Bachmann, 2006; Montgomery, 2008).

Sexual function in women is complicated and varies significantly through life. It is clear that several factors can influence sexual function such as systemic conditions including anaemia, hypothyroidism, autoimmune disease, chronic pain, age, menopausal status, medicine, alcohol intake and also low mood/depression (Arunakumari and Walker, 2009; Katz and Mazer, 2009). A longitudinal study of women in the peri-menopause and early menopausal phase showed a statistically significant decrease in sexual desire amongst this group compared to before this period of time began. Additionally, women who suffered worse menopausal symptoms, or had higher stress levels, were also more likely to have decreased sexual function (Woods et al., 2010). A strength of this study was that diaries for sexual activity and desire were filled in contemporaneously from the 1990's so this limited recall bias. Sexual desire has also been shown to decrease with age in a cross sectional population study in Australia with each decade from 20 to 70 years old showing a decrease in sexual desire within the cohort (Hayes et al., 2008). The same study showed that sexual distress was positively associated with depression (Hayes et al., 2008). The following commonly used drugs have been associated with a FSD: alcohol, hormonal contraceptives, antidepressants and anti-hypertensives (Arunakumari and Walker, 2009). This situation becomes even more complex when

considering chronic pain. It is often the case that these patients are treated with opioids, and therefore it may be difficult to ascertain whether the FSD is secondary to the chronic painful condition, the opioid treatment for it, or both.

2.5.1 Classification systems for FSD

Definitions of FSD are evolving continually. Currently there are five main classification systems in use. These are the Diagnostic and Statistical Manual of Mental Disorders (DSM) V, the International Classification of Diseases (ICD-10), International Conference on Women's Sexual Dysfunction, the Fourth International Consultation on Sexual Dysfunctions and the American Foundation of Urologic disease (American Psychiatric Society, 2013; Basson et al., 2001; Hatzimouratidis and Hatzichristou, 2007; McCabe et al., 2016; World Health Organisation, 2012). It is important when undertaking research to use a widely recognised definition for the condition being studied, because without this the results are not easily understood in a clinical context. ICD-10 and DSM V are the most widely used systems internationally (McCabe et al., 2016). The fact that there are several widely recognised classification systems and no single gold standard has made the research in the area relatively confused, with research using different definitions for the same condition. DSM V is mainly a psychiatric disorders classification system, but it has been adapted to define organic conditions, whereas ICD-10 splits disorders into organic and non-organic (American Psychiatric Society, 2013; McCabe et al., 2016; World Health Organisation, 2012). There are also several expert consensus definitions for FSD from conferences that are in use. These have taken ICD-10 and DSM V and expanded the definitions (Basson et al., 2001; McCabe et al., 2016). All the classification systems split sexual dysfunction into four main groups of problems

which include desire, arousal, orgasm and sexual pain. A summary of the conditions defined within each system can be seen in Table 2-3.

The most common form of FSD is loss of desire. This occurs when a woman suffers from either persistent or recurrent deficiency of sexual fantasies and desire for sexual activity which thereby causes the woman either personal or interpersonal distress (American Psychiatric Society, 2013; Basson et al., 2001; McCabe et al., 2016; Quirk et al., 2002; Rosen et al., 2000; World Health Organisation, 2012). Low desire conditions are described in slightly different ways by each of the classification systems (see Table 2-4). The common parts of the definitions are that the symptoms are required to cause personal distress, be persistent or recurrent (at least three- or six-months dependent on definition) and affect the woman on over 75% of occasions. Sexual arousal disorders do not preclude a woman from experiencing sexual enjoyment or arousal, but this must be absent on more than 75% of occasions.

	Desire	Arousal	Orgasmic	Sexual pain	Other	Further Info
ICD-10 (World Health Organisation, 2012)	Lack or loss of sexual desire Sexual aversion	Lack of sexual enjoyment Failure of sexual response	Orgasmic dysfunction	Non-organic vaginismus Dyspareunia	Excessive sexual drive	
DSM-V (American Psychiatric Society, 2013)	Female sexual interest-arousal disorder		Female orgasmic disorder	Genito-pelvic pain-penetration disorder	Substance or medicine induced disorder	Symptoms for 6 months on >75% of occasions causing clinically significant distress
4th international consultation on sexual dysfunction (McCabe et al., 2016)	Hypoactive sexual desire dysfunction	Female sexual arousal dysfunction	Female orgasmic dysfunction	Female genital-pelvic dysfunction Painful orgasm	Persistent genital arousal disorder Postcoital syndrome Hypohedonic orgasm	Present for three months, leads to distress occur in >75% of occasions
International consensus development conference on women's sexual dysfunction (Basson et al., 2001)	Hypoactive sexual desire disorder Sexual aversion disorder	Sexual arousal disorder	Orgasmic disorder	Dyspareunia Vaginismus Noncoital sexual pain disorder		Requires personal distress

Table 2-3 Summary of classification systems for female sexual dysfunction

Table 2-4 Desire disorder definitions from each classification system for FSD

Grading system	Desire condition	Description
Fourth international consultation on sexual dysfunction (McCabe et al., 2016)	Hypoactive sexual desire dysfunction	Persistent or recurrent deficiency of absence of sexual or erotic thoughts or fantasies and desire for sexual activity. In order to diagnose must cause distress.
International consensus conference on women's sexual dysfunction (Basson et al., 2001)	Hypoactive sexual desire disorder	Persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for or receptivity to sexual activity which causes personal distress. Sub grouped into lifelong vs acquired, generalised vs situational, aetiology (organic, psychogenic, mixed, unknown)
DSM V (American Psychiatric Society, 2013)	Female sexual interest-arousal disorder	Lack of or significantly decreased sexual interest or arousal is manifested by at least three of the following characteristics i) absent or decreased interest in sexual activities ii) absent or decreased sexual or erotic thoughts or fantasies iii) no or decreased initiation of sexual activity and typically unreceptive to a partners attempts to initiate iv) absent or decreased sexual excited or pleasure during sexual activity in almost all or all sexual encounters, v) absent or decreased sexual interest or arousal in response to any internal or external sexual or erotic cues vi) absent or decreased genital or non-genital sensations during activity in almost all or all sexual encounters
ICD-10 (World Health Organisation, 2012)	Lack or loss of sexual desire	Loss of sexual desire is the principal problem and is not secondary to other sexual difficulties. Lack of sexual desire does not preclude sexual enjoyment or arousal but makes the initiation of sexual activity less likely

2.6 Summary

This chapter has presented an overview of the core concepts that are important for the remainder of the thesis. The epidemiology of CNCP and opioid use has been discussed and the scale of the problem explored. Adverse effects of opioids have been discussed in general terms and the more specific sexual and reproductive effects and relevant physiology. This chapter provides the context for the remainder of the thesis.

3 Systematic review

3.1 Introduction

Reproductive and sexual dysfunction secondary to hypogonadism are recognised adverse events in men receiving opioids, and in women receiving illegal opioids, this has been discussed in depth in section 2.4.1 (Abs et al., 2000; Aloisi et al., 2009; Benyamin et al., 2008; Brown and Zueldorff, 2007; Daniell, 2002; Genazzani et al., 1993; Rubinstein et al., 2013; Schmittner et al., 2005; Smith and Elliott, 2012). This has been highlighted as an area for further research by both the British Pain Society and in a paper for the American Pain Society and American Academy of Pain Medicine highlighting research gaps (Chou et al., 2009b; Williams et al., 2013). The most appropriate initial step for investigating this potential link is to assess the current evidence available through a comprehensive systematic review of the literature. This chapter will present the methods and results of a systematic review investigating women aged 18-55 years old receiving long-term opioids for CNCP and potentially associated sexual and reproductive dysfunction. The results of the review will be used to determine relevant outcomes to be used in subsequent studies within the thesis.

3.2 Aims

To conduct a comprehensive systematic review of the published literature in relation to long-term opioid use for CNCP and potentially related endocrine adverse effects in women aged 18-55 years old, with a specific focus on reproductive and sexual dysfunction relating to hypogonadism (biochemical or clinical).

3.3 Methods

To undertake the systematic review, a search of the relevant databases was undertaken using a predefined search strategy. The papers included were selected based on inclusion and exclusion criteria defined in a systematic review protocol developed prior to starting the review, and these were applied to the title, abstract and full text (see Appendix 1). Papers included were reference checked, as were any literature reviews for relevant papers, to ensure that no potential papers that might be included were missed. Papers that met the inclusion criteria were assessed for quality using critical appraisal skills programme (CASP) checklists (Critical Appraisal Skills Programme (CASP), 2014). Data was extracted using a standardised proforma (see Appendix 2). The collected data was synthesised by the author (ER Emily Richardson).

3.3.1 Search strategy

A Search of the following databases was undertaken in October 2014:

1. MEDLINE – General Medical Database 1946 to present. Contains over 5,600 worldwide journals. MEDLINE includes a broad range of resources focusing on biomedicine and health (U S National Library of Medicine, 2014). Accessed via Ovid.
2. Embase – Excerpta Medica Database 1974 to present (strong in its coverage of drug and pharmaceutical research [Drug therapy and research, including pharmaceutics, pharmacology and toxicology] with over 22 million records, 7500 journals, 90 countries) (Elsevier, 2014). Research into use of databases for drug adverse effects has shown that Embase performs well, and uncovers

references that would not be found through MEDLINE alone (Biarez et al., 1991). The database was limited to exclude MEDLINE results. Accessed via Ovid.

3. TOXLINE – Toxicology Data Network 1965 to present. Specialised database that provides bibliographic information covering the effects (biochemical, pharmacological, physiological, and toxicological) of drugs and other chemicals, with over 4 million bibliographic citations (U S National Library of Medicine, 2013). The search excluded PubMed as these references will have been found through the Medline search. TOXLINE is accessed through its own internet interface.
4. PsychINFO – Psychology and allied fields 1806 to present. The scope of this database is mental health and behavioural science, and it contains over three million peer-reviewed articles, it was accessed via Ovid (American Psychological Association, 2014).
5. CINAHL – Cumulative Index to Nursing and Allied Health Literature 1981 to present. CINAHL is a database specific to nursing but also covers 17 other allied health professions (National Institute for Health and Care Excellence, 2014b). Accessed via Healthcare databases advanced search from NICE (HDAS NICE).
6. AMED – Allied and Complementary Medicine produced by the Health Care Information Service on the British Library. The scope of the database is journals in allied professions to medicine, complementary medicine and palliative care. 1985 to present (National Institute for Health and Care Excellence, 2014c). Accessed via Ovid.

7. Web of Science, a collection of databases allowing searching not only for publications, but for citations as well, which is accessed via its own internet interface (Keele University, 2014).

The search strategy was developed in partnership with other primary care clinicians, systematic reviewers and medical librarians. Appendix 3 presents the detailed search strategy for each database. This consisted of three search strands. Strand one searched for different types of opioid analgesics using generic terms such as narcotic/opioid analgesics and narrow drug name terms; this was adapted from a Cochrane review on the use of opioids in CNCP (Noble et al., 2010). Strand two searched for adverse effects as a generic term using a search strategy taken from a paper by Golder et al (2006), which developed adverse effects search filters for MEDLINE (~100% sensitivity) and Embase (~83% sensitivity). This was then adapted for use in the other databases searched. The final search strand looked at specific female reproductive and sexual adverse effects. These included conditions identified from a preliminary literature search, such as opioid induced hypogonadism, opioid induced androgen deficiency (OPIAD) and a wide range of female reproductive health related endocrine disorders.

There were limitations as to the length and type of search that could be done with some of the databases, and this led to differences between searches. The search in PsychINFO did not include the search strand for generic adverse effects as this decreased the search results significantly. There were papers known to the author (ER) that were not included in the search results, but when this strand was removed the papers appeared in the search results. Additionally, the search strand for adverse effects was developed and validated for MEDLINE and Embase not PsychINFO. The

search of AMED did not yield many results as this is not a database that focuses on conventional pharmacological treatments but rather alternative treatments. TOXLINE is a less sophisticated search engine allowing only a single search line, consequently the search strategy had to be considerably simplified.

Citation tracking

References from relevant papers were tracked, and the papers examined for whether they met the inclusion criteria. Any review papers that were revealed through the literature search were not included in the systematic review, but their references were searched for any relevant literature that had not already been identified through the database searches. The reference lists from full texts that were included in the systematic review, were also searched for any papers that were not found from the initial search. No extra papers were included following citation tracking.

3.3.2 Study selection

Papers identified through the database search and additional methods were then reviewed to see if they met pre-defined inclusion and exclusion criteria. These were applied to the title, abstract and then full text. Titles were assessed by a single reviewer (ER) and the abstracts and full texts were reviewed by two reviewers (ER and John Bedson (JB) or Ying Chen (YC)), with a third reviewer arbitrating on any conflicts of opinion (Kate M Dunn (KD)).

3.3.3 Inclusion criteria

Articles selected for inclusion in the systematic review fulfilled the following criteria:

- Population: Human females, aged 18-55 years old.

- If studies included males or females outside the age range the paper was included if stratified data was available.

- The age range was chosen to include women up to and including those going through the menopause. A preliminary literature search revealed that menopausal symptoms may be one of the potential reproductive adverse effects in women associated with long-term opioids (Daniell, 2008).
- Opioid use for CNCP defined as use for longer than one month.
    - There is no specific definition of long-term opioid use. Previous epidemiological studies have used a definition of long-term opioids as use for "longer than 90 days and associated with a total supply of at least 120 days, or with 10 or more opioid prescriptions of any type dispensed" (Campbell et al., 2010; Von Korff et al., 2008). It was shown that people who fulfilled these criteria were more likely to continue opioids for a year (Campbell et al., 2010; Von Korff et al., 2008). However, in a preliminary literature search, it was found that there was limited relevant literature available. Some of the literature that appeared relevant had taken one month of opioid treatment as their definition for long-term use. Consequently, a pragmatic decision was made to define chronic use as 'one month or more' to allow inclusion of as many potentially relevant papers as possible.

3.3.4 Exclusion criteria

The following criteria were used to exclude studies identified through the search.

- Non-human studies

- Methadone use for rehabilitation from illegal drug use with no chronic pain
- Illegal opioid users
- Cancer pain
- Non-pain conditions
- Non-English papers, where no translation was available
- Full text unavailable
- Systematic reviews/Review papers
- Editorials

All other study types were included.

3.3.5 Data extraction

Following selection of full texts to be included, a single reviewer (ER) extracted data using a standardised word proforma (appendix 2). The proforma was developed prior to identifying the papers with guidance from Keele University's Research Institute for Primary Care and Health Sciences systematic review team, and was based on other extraction forms developed from within the primary care research centre. Prior to completing the review, it was expected that there would be a wide variety of study designs included. Consequently, since the data extraction form needed to encompass all study types, not all of the information would be found for each included study. The form also included a section to record the study design. Data was extracted on the number of people included in each arm of studies, the types of outcomes recorded, results, quality assessment, authors' conclusions, and reviewers' comments on the papers included.

3.3.6 Quality assessment

Prior to starting the literature review and developing the protocol it was decided that it was important to include a wide variety of studies to ensure full representation of the evidence available. Consequently, it would be important to have a consistent way of assessing quality. There is no gold standard for quality assessment of observational studies included in systematic reviews and when quality assessment is undertaken, a tool developed by the reviewer is often used (Mallen et al., 2006). The centre for reviews and dissemination (CRD) at York University produce guidelines on undertaking systematic reviews. These suggest that there is no perfect instrument to assess quality in reviews on adverse effects, as these often include different study designs and no single assessment checklist will be appropriate for all the included studies. The CRD recommend using validated assessment criterion, and the reason for quality assessment should be clear to the author prior to commencing (Centre for Reviews and Dissemination, 2009). CASP checklists were used to assess the quality of the papers included as they offer tools for different study types, but as they are all developed by the same team, they follow a similar format (Critical Appraisal Skills Programme (CASP), 2014). A checklist was completed for each of the papers apart from the single case reports for which there is no CASP quality assessment tool. Case studies provide low quality evidence and the Oxford Centre for Evidence Based Medicine does not include them in their grading system for level of evidence (Glasziou et al., 2003; Howick et al., 2011). Case reports are not, however, to be completely ignored; they provide evidence on previously un-investigated areas, and generate hypotheses for rare adverse effects from common treatments. In addition, a systematic review of case reports can provide appropriate evidence for rare harms. Case reports are subject to publication bias, as a case report with negative findings

would never be written (Centre for Reviews and Dissemination, 2009). CASP checklists do not give a grade of evidence once completed but do provide an idea of whether the results presented are reasonable and highlight limitations in the studies.

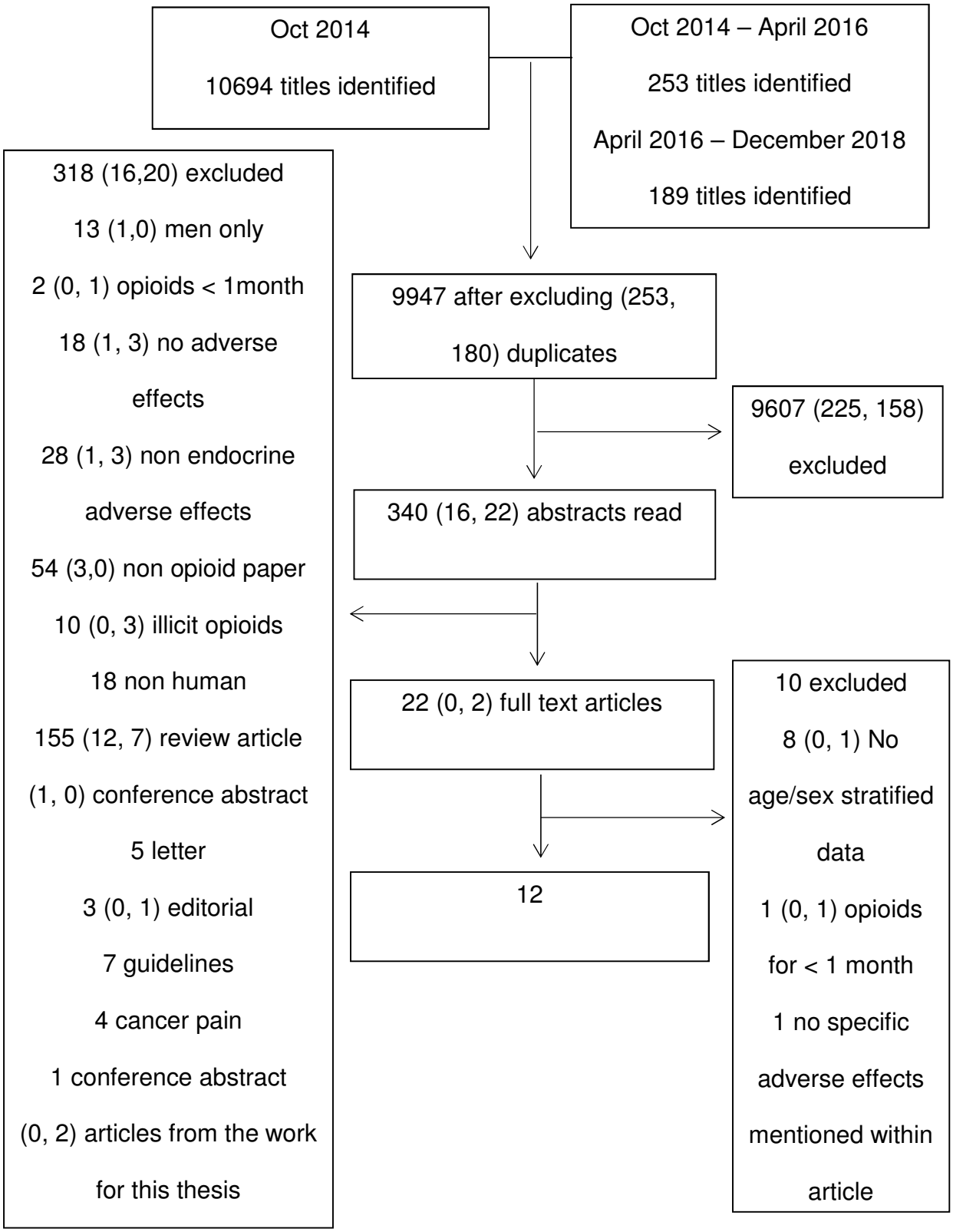
3.4 Results

3.4.1 Studies identified

The search returned 10694 papers (Embase 4088, Web of Science 3120, MEDLINE 1664, TOXNET 1432, PsychINFO 270, CINAHL 110, and AMED 10), after excluding duplicates this reduced to 9706 and the titles of these were screened by a single reviewer (ER). 361 titles appeared to meet the inclusion criteria and these abstracts were included for review. Abstracts were reviewed by ER and one other (JB or YC) to assess whether they met inclusion/exclusion criteria. Any disagreements were decided by a third reviewer (KD) and 22 papers were identified for inclusion. The full texts were then screened by a single reviewer, and 12 papers were included in the final review (See Figure 3-1). An updated search in April 2016 identified 241 additional papers (253 prior to excluding duplicates), of which 225 were excluded based on title; the remaining 16 abstracts were reviewed and no full texts were included (one paper men only, one discussed no adverse effects, one did not mention endocrine adverse effects, 12 review articles and one conference abstract). A further update was undertaken in December 2018 and this identified a further 189 titles (180 after removal of duplicates), 22 abstracts were reviewed (three replacement opioid therapy, two not long-term opioids, one no specific adverse effects, seven review articles, one risks during pregnancy, one editorial, three treatment of OPIAD, one non reproductive adverse effects, two were publications of

work from this thesis), two full texts were reviewed. Neither full text was included in the review since one did not separate results by sex and age, and the other full text did not describe duration of opioid use.

Figure 3-1 Flow chart showing results of systematic search and selection of included studies. Numbers in brackets are those for each category from the updated search; the first number is the 2014-16 search and the second 2016-18.



3.4.2 Quality assessment

The main limitations of the papers were small numbers of participants, and subsequently the subgroups of interest were not powered for statistical analysis. Recruitment was on the whole well described, but in the case of Daniell (2008) recruitment was not systematic and controls were paid. Data was collected for the most part using validated questionnaires or laboratory measurements of hormones. There were some drawbacks to hormone measurements as they were not synchronised with the menstrual cycle, this will affect the results due to the natural variation in hormones throughout the cycle. The results of the CASP checklist highlighting strengths and limitations of each paper is summarised in Table 3.1.

3.4.3 Study characteristics

The studies included considered a variety of methods of opioid delivery, including oral (six studies), intrathecal (five studies) and transdermal (one study). Oral opioids are tablets or liquids taken by mouth. Intrathecal opioids are given long-term through use of a pump with a catheter (tube) inserted into the spinal canal. Intrathecal opioids are delivered directly to central opioid receptors and avoid the blood brain barrier, which means much lower doses of opioids are required. Transdermal opioids are delivered via a patch placed on the skin and provide a constant amount of opioid throughout the day through absorption into the capillary system.

One cohort study, four case control studies, four cross-sectional studies, one case series and two single case reports were included. The studies all had small numbers of participants with a maximum of 41 patients in the case arm of one of

the papers. These small numbers were partly due to the narrow range of this review, as only women under 55 years old could be included (often the studies had larger numbers but this included males and older women). In total there were only 165 patients included in all the studies (including 35 controls). The length of time that patients were followed-up for after commencing opioids was variable, ranging from a minimum of one month up to 12 years. The outcomes observed were either clinical (menstrual abnormalities and decreased libido), or biochemical (measurements of sex hormones LH, FSH, oestrodiol, progesterone, dehydroepiandrosterone sulphate (DHEAS), free testosterone (fT), total testosterone (TT), prolactin (PRL), sex hormone binding globulin (SHBG) and a GnRH stimulation test measuring subsequent levels of LH and FSH). In the majority of papers, both clinical and biochemical aspects were investigated. A proportion of the results were not stratified for age or gender and therefore were not included in the review. A summary of the papers and their main findings can be found in Table 3-1.

Table 3-1 Summary of papers included within the systematic review (age presented in years)

Author, Year, Location (reference)	Design	Authors summary of findings	Quality assessment from CASP checklists.
	Intrathecal opioids		
Abs et al., 2000 Belgium (Abs et al., 2000)	Case-control study. Setting: Pain clinic. Duration of treatment: 26.6 +/- 16.3 months. Sample Size: Cases N = 21 and controls N = 3 Opioid: Morphine or Hydromorphone Age: 49.2 (± 11.7), 21 premenopausal women included	Neuroendocrine dysfunction (clinically and biochemically) following opioid use. Obvious difference in hormonal levels between case and control in premenopausal women but did not reach significance due to small numbers within the subgroup.	Positives: matched for chronic pain. Validated questionnaire and hormone levels. Negatives: Selection criteria not described. Larger numbers needed for statistical analysis, no power calculation performed. Missing data reasons not described.
Finch et al., 2000 Australia (Finch et al., 2000)	Case-control study (No controls for women < 45 years old so considered as cross-sectional). Setting: Pain clinic. Duration of treatment: 0.02-8 years (median 2.5). Sample Size: N = 7 Opioid: Morphine Age: 38.3 (±1.5) (mean ± SEM)	Small doses of intrathecal morphine have a profound effect on the HPG axis so patients should be monitored.	Positives: selection of 30 sequential patients from pain clinic. Negatives: No control for women < 45 years old so no longer case-control. One time hormone measures.

N=number included, SEM = Standard error of the mean, S.D = standard deviation

Author, Year, Location (reference)	Design	Authors summary of findings	Quality assessment from CASP checklists.
Roberts et al.,2001 Australia (Roberts et al., 2001)	Cross-sectional study. Setting: Pain clinic. Duration of treatment: minimum 6 months. Sample Size: N = 15 Opioid: Morphine, hydromorphone, sufentanil Age: 53.4 (±1.4, range 28-88), 15 premenopausal women	HPG axis affected but requires further detailed assessment. This should be discussed with patients.	Positives: 80% response rate. Questionnaire validated. Negatives: Retrospective data collection. Scant data for premenopausal females. Missing data not explained (in reported data for women <50 years old, one reports 14 women included and another 15).
Njee et al., 2004 France (Njee et al., 2004)	Cross-sectional study. Setting: Pain clinic. Duration of treatment: 54 +/- 39.8 months (4-144). Sample Size: N = 10 Opioid: Morphine Age: 43.8	No evidence of permanent HPG suppression. Transient amenorrhoea, not accompanied by hormonal assays supportive of HPG suppression.	Negatives: retrospective data collection. Only minor focus on endocrine adverse effects and collected via a questionnaire which was not described and may not have been validated.
Kim et al., 2014 United States (Kim et al., 2014)	Case series. Setting: Pain clinic. Duration of treatment: 12 months and 24 months. Sample Size: N = 2 Opioid: Morphine Age: 43 and 46	Two female patients < 55 years old were both androgen deficient on hormone assays. Androgen deficiency is common in patients treated with intrathecal opioids for CNCP.	Positives: consecutive patients recruited Negatives: Only two patients in age range, was undertaken as a cohort study, but assessed as a case series. Questionnaire used was not described and may not have been validated.

N=number included, SEM = Standard error of the mean, S.D = standard deviation

Author, Year, Location (reference)	Design	Authors summary of findings	Quality assessment from CASP checklists.
	Oral opioids		
Mussig et al., 2007 Germany (Mussig et al., 2007)	Case report. Setting: Endocrine clinic. Duration of treatment: 4 months. Sample Size: N = 1 Opioid: hydromorphone Age: 32	Hypogonadism when receiving hydromorphone which resolved when changed onto tramadol	Negative: Single case reported because of positive effect of treatment change.
Daniell, 2008 United States (Daniell, 2008)	Case-control study. Setting: Primary care Duration of treatment: Minimum 1 month. Sample Size: Case N = 21, Control N = 16 Opioid: methadone, morphine sulphate, oxycodone, transdermal fentanyl (in two cases) Age: Cases 39.3 (±4.9 S.D.) Controls 42.7 (±3.5)	Hormonal assays were 48-57% lower in opioid treated women (fT, TT, oestrodiol, LH, FSH, DHEAS) compared to controls. Statistically significant for TT, fT, oestrodiol and DHEAS. Amenorrhoea cases: 52%, controls: 20%, $p < 0.05$.	Positives: No drop outs as one time measurement. Negatives: Controls not well matched (chronic pain, statistically different for BMI (body mass index), smoking status and age). Results not split for oral or transdermal opioid delivery.
Fraser et al., 2009 Canada (Fraser et al., 2009)	Cross-sectional study. Setting: Pain clinic. Duration of treatment: 5.5 years (+/- 3 years) Sample Size: N = 14 Opioid: daily morphine-	Lower rate of hypogonadism than expected. 21% of women had hypogonadism.	Positives: interviews by a single interviewer with a set method. Negatives: hormone assays not timed to cycle. Single measurement.

N=number included, SEM = Standard error of the mean, S.D = standard deviation

Author, Year, Location (reference)	Design	Authors summary of findings	Quality assessment from CASP checklists.
	equivalent dose 679 ± 620mg Age: 38.6 (± 7.2)		
Reddy et al., 2010 England (Reddy et al., 2010)	Case report. Setting: Endocrine clinic. Duration of treatment: 7 years Sample Size: N = 1 Opioid: Morphine Age: 37	Hypogonadism clinically and biochemically.	Negative: Single case reported because of clinical findings.
Rhodin et al., 2010 Sweden (Rhodin et al., 2010)	Case-control. Setting: Pain clinic. Duration of treatment: at least 1 year. Sample Size: Case N = 16, controls N = 6 Opioid: methadone, morphine, oxycodone Age: 48 (32-63), split into women < 50 but no average age given	HPG axis disruption with sexual disturbance and menstrual irregularities.	Positives: Validated questionnaire. Clinical and biochemical results correlate. Control group had chronic pain. Enough power to show statistical significance. Negatives: small numbers, 3 women receiving opioids on HRT, 0 in control group.
Wong et al., 2011 Canada (Wong et al., 2011)	Case-control. Setting: Pain Clinic. Defined chronic pain as pain for > 6months. Duration of treatment: No	A significant decrease in fT in patients with low libido and a non-significant decrease in DHEAS but not correlated with symptoms of hypogonadism.	Positives: Matched for chronic pain Negatives: Data only partly stratified for pre-menopausal women. Exact length of time on opiates not reported. Recall bias asked to

N=number included, SEM = Standard error of the mean, S.D = standard deviation

Author, Year, Location (reference)	Design	Authors summary of findings	Quality assessment from CASP checklists.
	minimum stated. Sample Size: Cases N = 30, controls N = 10 Opioid: not described Age: 53 (28-83), included 30 premenopausal women		compare current sexual desire to that before opiates.
		Transdermal opioids	
Aurilio et al., 2011 Italy (Aurilio et al., 2011)	Open prospective cohort study. Setting: pain clinic. Duration of treatment: 6 months Sample Size: N = 8 Opioid: Buprenorphine Premenopausal women. Mean age 39.5 (26-50)	No strong endocrine impairment. No changes in menstrual cycle reported and hormone levels were stable or increasing.	Positives: hormone levels used as outcomes and six month follow-up, repeated measures from same patient at four time points. Negatives: small numbers, demographics of group not described. Hormone sampling not timed to cycle.

N=number included, SEM = Standard error of the mean, S.D = standard deviation

3.5 Study results

The following section will discuss the evidence found for disruption of the HPG axis, in the form of sexual and reproductive dysfunction. Clinical and biochemical outcomes have been reported within the papers, and as such the results have been presented split into these two groups.

3.5.1 Clinical outcomes

The clinical outcomes that were included in the studies were alteration in menstrual cycle and libido. The findings are summarised in Table 3-2.

Menstrual Cycle

Ten studies looked for changes in menstrual cycle as a marker for hypogonadism, and defined any changes as either amenorrhoea or oligomenorrhoea which were explained in section 2.4.1. Daniell (2008) undertook a case-control study, which was the only paper included in the review that showed a statistically significant difference in the menstrual cycle between those taking oral opioids (52% who developed non-surgical amenorrhoea) and controls (20%, probability (p) <0.05). The rate of amenorrhoea found in controls (20%) was higher than would be expected for the general population (3-4%) suggesting the controls may not be a representative of the general population (The Practice Committee of the American Society for Reproductive Medicine, 2008). Controls were not well matched to those taking opioids, with statistically significant differences in age (controls older), smoking status (controls smoked less), BMI (controls had a lower BMI) and they were not matched for chronic pain. The other oral studies that reported data on menstrual cycles were Fraser et al (2009) which was a cross-sectional study and found 23% (3/13) of women developed oligo/amenorrhoea following commencing

opioids. Rhodin et al (2010) undertook a case-control study, and found amenorrhoea in 81% (13/16) of cases and 0% (0/6) of controls (no statistical analysis given). There were two case studies both reporting amenorrhoea whilst taking long-term oral opioids, and one showing resolution of amenorrhoea with decreasing dose of hydromorphone with conversion to tramadol (a less potent opioid).

Four of the papers on intrathecal opioids reported on menstrual status, showing oligo/amenorrhoea in 67% (14/21) (Abs et al., 2000), 71% (5/7) (Finch et al., 2000), 31% (4/13) (Njee et al., 2004) and 47% (7/15) (Roberts et al., 2001) of those treated with opioids. In one study, the menstrual cycle irregularities that were present at the start of treatment resolved by 4-8 months of treatment (it was unclear if this was an issue preceding treatment or following treatment) (Njee et al., 2004). Abs et al (2000) also looked at the menstrual cycle in three control patients and each of these continued to have a regular cycle, but no statistical analysis was made due to the small number of subjects. One study examined eight premenopausal women using transdermal opioids and found no reported alteration in menstruation (Aurilio et al., 2011). The data across the studies suggest that 23% to 71% of women taking oral or intrathecal opioids may be affected by oligo/amenorrhoea. However, those taking transdermal opioids did not appear to suffer with this particular adverse effect (Abs et al., 2000; Finch et al., 2000; Njee et al., 2004; Roberts et al., 2001).

Libido

Three papers reported on the status of libido for premenopausal women. Wong et al (2011) found no statistical difference in decreased libido, with 61% (19/31) of cases taking oral opioids reporting decreased libido and 70% (7/10) of controls (p

= 0.62). However, Roberts et al (2001) found low libido in 71% (10/14) of those receiving intrathecal opioids, and Finch et al (2000) found low libido in 100% (7/7) of those commencing treatment. Other studies did provide information on libido but this was not stratified for age or gender so could not be included in the review.

Table 3-2 Summary of clinical effects within the systematic review.

Sign/Symptom	Study	Result
Amenorrhoea		
Intrathecal Studies	Abs (2000)	67% (14/21) cases amenorrhoea, 0% (0/3) controls
	Finch (2000)	71% (5/7) amenorrhoea
	Njee (2004)	31% (4/13) amenorrhoea resolving by 4-8 months of treatment
	Roberts (2001)	47% (7/15) oligo/amenorrhoea
Oral Studies	Daniell (2009)	52% cases non-surgical amenorrhoea, 20% of controls, $p<0.05$
	Fraser (2009)	23% (3/13) oligo/amenorrhoea
	Mussig (2007)	1/1 amenorrhoea, at 3 months on opioids resolution of amenorrhoea on removal of opioid
	Rhodin (2010)	81% (13/16) cases amenorrhoea, 0% (0/6) controls
	Reddy (2010)	1/1 amenorrhoea for 7 years on opioids
Transdermal Studies	Aurilio (2011)	0/8 reported altered menstruation
Decreased Libido/Sexual Desire		
Intrathecal Studies	Roberts (2001)	71% (10/14)
	Finch (2000)	100% (7/7)
Oral Studies	Wong (2011)	61% cases, 70% controls $p=0.62$

3.5.2 Hormonal

This section will report the results of the hormonal assays completed within the studies, it will be divided by route of administration of opioids. 10 studies reported on hormonal assays, they include three intrathecal opioid studies (Abs et al., 2000; Finch et al., 2000; Kim et al., 2014), six oral studies (Daniell, 2008; Fraser et al., 2009; Mussig et al., 2007; Reddy et al., 2010; Rhodin et al., 2010; Wong et al., 2011) and one transdermal opioid study (Aurilio et al., 2011) and are summarised in Table 3-3.

Intrathecal Opioids

Abs et al (2000) performed a case-control study that showed levels of LH, FSH and oestrodiol that were at the low end of normal in current opioid users and normal levels in controls, this difference was not statistically significant. Low levels of progesterone were found in the opioid treated group, which were lower than in the control group, the difference was not statistically significant. Finch et al (2000) looked at the hormone levels (oestrodiol, FSH and LH) of seven premenopausal women and found levels of oestrodiol and FSH that were at the bottom end of normal and low levels of LH. Kim et al (2014) focused on measuring TT, fT and DHEAS levels and had two cases with low hormone levels, the author labelled them as androgen deficient. Finch et al (2000) found that the subjects treated with opioids in the majority of cases had hormone levels in the low end of normal which were lower than in controls.

Oral Opioids

Daniell (2009), Rhodin et al (2010) and Wong et al (2011) all undertook case-control studies giving a statistical analysis of their results. Daniell (2009) found a

statistically significant ($p<0.01$) decrease in TT, fT, oestrodiol and DHEAS in opioid users, however even though there was a difference in these hormones between cases and controls, those treated with opioids still had levels within the normal range. Rhodin et al (2010) also showed lower hormone levels in the treatment group (oestrodiol, FSH, LH and post GnRH stimulation LH and FSH) which were statistically significant for oestrodiol ($p = 0.05$) and LH peak post GnRH stimulation ($p=0.01$). Contrary to this, Wong et al (2011) found no statistically significant difference in hormone levels between treatment and control groups in premenopausal women, but they focused on different hormones including fT, TT, PRL, DHEAS and SHBG. Fraser et al (2009) undertook a cross-sectional study and showed low normal levels of all the hormones tested for (TSH (thyroid stimulating hormone, a hormone that is not related to the HPG axis), LH, FSH, SHBG, Oestrodiol and Progesterone). The final two studies were case reports both showing low or low normal levels of FSH, LH and oestrodiol; Mussig et al (2007) showed negative correlation of oestrodiol level to morphine plasma levels ($r = -0.6$, $p = 0.03$) as they withdrew hydromorphone and replaced it with tramadol (a weaker opioid) (Mussig et al., 2007; Reddy et al., 2010).

Transdermal Opioids

Aurilio et al (2011) measured hormones at baseline and throughout treatment of up to six months with transdermal buprenorphine. They found no statistically significant change in hormone levels (LH, FSH, TT and fT) during this period.

Table 3-3 Summary of hormonal effects within the systematic review.

Sign/Symptom	Study	Result
Hormone Effects		
Intrathecal Studies	Abs (2000)	21 cases 3 controls. Low normal levels of LH, FSH and oestrodiol and low progesterone in cases compared with normal in controls. Did not reach significance. Small numbers.
	Finch (2000)	7 cases no control. Low normal levels of oestrodiol and FSH, low LH.
	Kim (2014)	2 cases with low levels of testosterone, free testosterone or DHEAS author describes them as androgen deficient.
Oral Studies	Daniell (2009)	21 cases, 16 controls statistically significant decrease in TT, fT, oestrodiol, DHEAS. The mean values for all hormones were still within normal limits.
	Fraser (2009)	14 cases. Normal levels of TSH, LH, FSH, SHBG, oestrodiol and progesterone.
	Mussig (2007)	1 case. LH, FSH and oestrodiol all increased with decreasing opioid dose. Oestrodiol showed a negative correlation with morphine plasma levels r= -0.6, P=0.03.
	Reddy (2010)	1 case. Low levels of LH, oestrodiol, PRL, low normal FSH.
	Rhodin (2010)	16 cases, 6 controls. Statistically significant decrease in oestrodiol and LH peak after GnRH stimulation. FSH, LH and FSH peak post GnRH lower than in control but do not approach statistical significance. Levels within normal range.
	Wong (2011)	29 cases, 9 controls. No statistically significant difference overall for any hormone levels in premenopausal women. (fT, TT, PRL, DHEAS, SHBG). In those with low libido cases had a statistically significant decrease in TT (p = 0.04)
Transdermal Studies	Aurilio(2011)	N=8. No statistically significant change in hormone levels (LH, FSH, TT, fT) from baseline to 6months.

3.5.3 Sensitivity analysis

A sensitivity analysis was undertaken comparing the results for women aged 18-55 years old and those aged 18-45 years old, in order to remove women in the peri-menopause from the analysis. When women were split into pre and post-menopausal within the data this was used as the cut off. The results were similar in the different age groups and menopausal states. The results of the sensitivity analysis can be seen in Appendix 4.

3.6 Discussion

3.6.1 Summary of main findings

The systematic review identified 12 studies in total. Of the studies included, five were case-control, three cross-sectional, two case reports, one case series and one cohort study. The papers looked at three different methods of opioid delivery; oral (five studies), intrathecal (six studies) and one study with topical buprenorphine. The outcomes reported were changes in hormone levels, menstrual cycle and libido. Clinical and biochemical changes were found in women taking oral or intrathecal opioids but these were not replicated in those women receiving transdermal buprenorphine.

Hormone levels in the case-control studies for oral (three studies) and intrathecal (one study) opioids were found to be lower in cases than in controls and statistically significant in two studies, however the hormone levels were still within normal laboratory range in some cases (Abs et al., 2000; Daniell, 2008; Rhodin et al., 2010; Wong et al., 2011). The studies that showed hormone levels within normal range still often found these levels were associated with clinical symptoms (Abs et al., 2000).

This contrasted with those in the transdermal study who showed no statistically significant change in hormone level when compared with baseline (Aurilio et al., 2011).

Oligo/amenorrhoea was observed in 23-81% of patients taking oral or intrathecal opioids (six studies) with Daniell (2008) showing a statistically significant difference between those taking opioids and controls (Abs et al., 2000; Daniell, 2008; Finch et al., 2000; Fraser et al., 2009; Njee et al., 2004; Rhodin et al., 2010; Roberts et al., 2001). These results again were found to be different to those receiving transdermal buprenorphine in whom none of the exposed women reported altered menstruation (Aurilio et al., 2011). Three studies reported data for libido and found low libido in 61-100% of women with one study comparing libido with controls finding no statistically significant difference (Finch et al., 2000; Roberts et al., 2001; Wong et al., 2011).

3.6.2 Strengths and limitations

Systematic review

The strengths of the review are that it was undertaken systematically with a predefined search strategy, inclusion/exclusion criteria and data extraction form. Firstly, the search protocol will be discussed, this was developed in conjunction with systematic review specialists. The search was developed based on a search protocol for an opioid Cochrane review and a search for adverse effects (Golder et al., 2006; Noble et al., 2010). The literature was also searched to ensure that the most appropriate databases were used, which led to the inclusion of the database TOXLINE as this is a specific database for adverse drug effects. The search strategy was comprehensive and produced a large number of results. No further papers were found through citation checking. Inclusion and exclusion criteria were developed a

priori then applied to abstracts and full texts by two independent reviewers. Any disagreements were referred to a third reviewer helping to prevent inconsistencies in how the criteria were applied and improving reproducibility.

Including case studies in the systematic review is a limitation since with this type of report there is the potential for publication bias. A decision prior to starting the review was taken to include all publication types except for review papers, conference abstracts and editorials. A preliminary search had shown low numbers of papers in the area of interest, and it was felt that it was important to include as many potential papers as possible in the review. Publication bias with case reports occurs because case reports often report a link in clinical findings and therapy. These can act as a stimulus for further research; however negative findings are not published because this would not justify the case report in the first instance. One of the studies was a case series, but due to the study inclusion criteria only two of eight patients were included in the review. However, this evidence is more reliable than from a case report, as the patients were selected systematically from a sample attending a pain clinic (Kim et al., 2014).

A meta-analysis was not undertaken due to the wide variation in studies included. In the systematic review protocol it stated that a meta-analysis would be undertaken if possible, primarily with the laboratory hormonal assays. Unfortunately, due to the variety of hormonal markers used and the different routes of administration, there were only two papers in the intrathecal and oral arms of the review that included some of the same hormone assays (excluding case studies). This would not have been appropriate for a meta-analysis.

Papers included in the study

All the studies included in the review have their limitations; this is partly due to the practicalities of undertaking a study in analgesia, as it would be unethical to withhold analgesics from a patient in chronic pain, in order to use them as a control subject. The review had a narrow remit and therefore included only a small subset of the subjects (women aged 18-55 years old) from papers that had small numbers to begin with. In total across all the papers included there were less than 200 cases and only 35 controls that could be included in the review. These small numbers lead to some difficulties with the analysis for the authors of the papers, particularly when trying to show statistical significance. For instance Abs et al (2000) found a difference in hormone levels between cases and controls, but probably due to the small numbers involved (21 cases, three controls) this was not statistically significant.

The studies were on the whole set within secondary care pain clinics (or from cases presenting to secondary care endocrinology clinics, one of 12 studies was set in primary care). This decreases the generalisability of the findings of these studies to the general population. A study within Europe showed that only 23% of patients with chronic pain were seen by a “pain specialist”, and the rest were managed in primary care. Consequently the participants in the majority of the studies represent a subset of chronic pain patients and they are likely to have had pain for longer than those presenting to general practice (Breivik et al., 2006). A study in Germany showed a median time of 12 years from pain onset to being seen in a specialist pain clinic (Schulte et al., 2010). Given the demographics of those attending pain clinic there is a potential for them to be systematically different from the general population of pain patients attending primary care.

Matching of cases and controls was an area with the potential to introduce bias, and often did not account for possible confounding factors such as chronic pain. Daniell (2008) recruited the cases and controls through public solicitation, and from the private practice of other medical practitioners. The sample is therefore drawn from the local general population; however the recruitment does not seem to have been systematic and those taking part as controls were offered a monetary reward and copies of their endocrine blood results. This raises the possibility of whether or not the controls had their own reasons to want hormonal investigation, perhaps financial or clinical, and if so, this becomes a potential confounding factor. The reliability of this study is limited as the controls were not well matched to those taking opioids, with statistically significant differences in age (controls older), smoking status (controls smoked less), BMI (controls had a lower BMI) and controls were not matched for chronic pain. All of these are confounding factors, which could potentially affect menstrual cycle and therefore the reliability of the results of this study (Daniell, 2008).

Another limitation affecting generalisability to a UK primary care population is that five of the studies were based on intrathecal opioids. UK national guidance suggests in the case of CNCP that this treatment should be administered in secondary care, under the supervision of a multidisciplinary pain team (The British Pain Society, 2008). This management strategy is not one that is deliverable in primary care, however patients do continue to live and function in the community where any potential adverse effects will manifest themselves, and if significant are likely to be brought to the attention of their GP.

Those studies that used questionnaire data collected this retrospectively introducing the possibility of recall bias, which is unlikely to be significant in terms of the

menstrual cycle but in terms of libido may be affected. It is often recommended that questions should not be asked about a period of time more than six months previously unless about significant life events e.g. deaths, and in several of the papers the follow-up time after commencing opioids was much longer, in one case up to 14 years (Abs et al., 2000; Bowling, 2004; Daniell, 2008; Finch et al., 2000; Fraser et al., 2009; Kim et al., 2014; Njee et al., 2004; Rhodin et al., 2010; Roberts et al., 2001; Wong et al., 2011).

Consistency in measuring hormone levels in premenopausal women can be problematic, because of the fluctuation in hormone levels that occurs during the menstrual cycle (Brook and Marshall, 2001). The majority of the studies included did not measure hormones at specific times in the cycle. Aurilio et al (2011) attempted to ensure that hormonal assays were taken within the same phase of the cycle. Despite this, however, large variations in oestrodiol levels were found between follow-up tests, indicating that this technique did not fully account for natural variations in hormones throughout the cycle. Several studies (including the two case studies) recognised the importance of timing hormone measurements to menstrual cycle, but because their patients were either oligo/amenorrhoeic or were expected to have hypogonadism, samples that had no relation to the menstrual cycle were used (Daniell, 2008; Fraser et al., 2009; Mussig et al., 2007; Reddy et al., 2010; Rhodin et al., 2010). Other studies tried to account for hormone (LH and FSH) variability in different ways, either through serial samples 15 minutes apart, GnRH stimulation tests, or samples taken at a specific times of the day (Abs et al., 2000; Rhodin et al., 2010; Wong et al., 2011). Kim,C. et al (2014) and Finch et al (2000) do not discuss this so it is likely their sampling method was unsystematic (Finch et al., 2000; Wong

et al., 2011). Various methods were undertaken to try to account for hormonal variation within the cycle, but none of these are completely satisfactory and limitations still exist.

3.6.3 Confounding factors

As mentioned in chapter two, the symptoms of HPG axis disruption can be caused by a variety of other conditions and medicines as well as potentially by long-term opioid use. CNCP is a potential cause for some of the symptoms reported such as decreased libido, and a significant issue with the studies examined was the way in which they accounted for the effect of chronic pain. CNCP can have a wide ranging impact on a patient's life, both physically and emotionally. In this case, confounding by indication is the primary issue, since it might be that not only the opioids prescribed for the painful condition cause potential adverse effects, but the painful condition they were prescribed for in the first instance might cause them as well, such as decreased libido (Katz and Mazer, 2009). For example the cross-sectional studies did not account for the CNCP as a causative factor, having only measured hormone levels once whilst on treatment (except Aurilio et al 2001 who took serial assays at baseline and up to six months). The studies could have partially accounted for the effect of CNCP by taking pre and post treatment hormonal assays and using the subject as their own control. The data shows that the patients included in the studies did indeed have decreased libido, but it is likely that this may be related not just to opioids but to the presence of CNCP. For example, in the case of Wong et al (2001) there was a non-significant difference when compared to the control group who were receiving non-opioid analgesics for pain.

One way to overcome confounding by indication is to use control subjects that are as closely matched as possible. Five case-control studies attempted to address this through the use of matched controls, however one of these had no controls in the age group of the systematic review, and therefore was included as a cross-sectional study (Finch et al., 2000). Out of the remaining four, three were matched for CNCP. None described this in detail but Rhodin et al (2010) said they matched for a comparable pain syndrome, Wong et al (2001) chose consecutive patients attending pain clinic, and Abs et al (2000) pain of similar duration and character. However, they did not match the subgroups for other factors. Abs et al (2000) did present data showing no statistically significant difference between cases and controls (Abs et al., 2000; Rhodin et al., 2010; Wong et al., 2011). Daniell (2008) selected controls that did not necessarily suffer from chronic pain, since patients were selected from the general population and their inclusion or exclusion was not dependent on them having CNCP. There were statistically significant differences between the case and control groups with the controls being older ($p < 0.002$), less likely to smoke ($p < 0.001$) and have a lower BMI ($p < 0.002$) than those taking opioids within the study. The author acknowledged these differences and provided evidence as to why he did not believe this influenced the results.

3.6.4 Clinical implications

The evidence reviewed appears to indicate that there is a potential relationship between long-term opioid use and reproductive and sexual dysfunction in women. The studies are limited, but show that clinically women may report amenorrhoea and loss of libido, both of which could potentially be associated with infertility. The implications of the findings from this systematic review are important for shared

decision making, and these potential adverse effects should be included when discussing long-term opioids with premenopausal women. This is also clinically important in the follow-up of patients on long-term opioids, as clinicians might need to include questions relating specifically to potential sexual and reproductive adverse effects. Patients may also be more likely to volunteer this information if they are aware there is a possible link with their medicine. It may also be important to discuss contraception with these women as opioids are not recommended during pregnancy unless the benefits outweigh the potential risks.

Aurilio et al (2011) studied transdermal opioids and found that hormonal measurements did not decrease with their use. This was reflected in their clinical findings, with no patients reporting menstrual disorders. This compares with the other studies of oral and intrathecal opioids, which showed decreased hormone levels that in some cases were statistically significant. It is important to remember that topical buprenorphine is not only different to the other opioids administered due to the route but also in the way buprenorphine works as it is a mixed agonist-antagonist which is explained further in section 2.3 (Walsh and Eissenberg, 2003). Another possible reason for this difference in adverse effects could be the equivalent dose of morphine/day prescribed for which there is no data from the systematic review. This potential difference will need investigating further because if this difference is reproducible, it would provide a safe means of treating premenopausal women with opioids, without altering their HPG axis clinically or biochemically.

The link to HPG axis disruption does appear to be strongest in patients commencing on intrathecal opioids. If use of this route of administration increases in the future, it may be necessary to introduce pre-treatment, and sequential in-treatment hormonal

assays to prevent clinically adverse effects that might be heralded by changes in the hormonal assays. This is also a consideration for when designing future studies so that patients might act as their own controls and offer a time varying covariate by which clinical changes might be assessed.

3.6.5 Comparison with existing literature

This literature review has found similar results to the current literature for men and illegal opioid use in women. A systematic review in men receiving regular opioids regardless of type found low testosterone in regular users when compared to controls (Bawor et al., 2015). Research in women taking illegal opioids and receiving opioids for treatment of heroin addiction have previously found menstrual disturbances, decreased sexual desire, infertility and reductions in LH and FSH levels (Afrasiabi et al., 1979; Pelosi et al., 1974; Smith and Asch, 1987; Stoffer, 1968). The systematic review undertaken for this thesis has found that women treated with prescribed long-term opioids appear to be affected by symptoms of reproductive sexual dysfunction which is also related to decreases in hormone levels. Hormone levels are often still within the normal range so cannot truly be thought of as hypogonadism, in comparison with men where low testosterone levels are an established adverse effect through suppression of the HPG axis (Ballantyne and Mao, 2003; Brennan, 2013; Brown and Zueldorff, 2007; Colameco and Coren, 2009; Katz and Mazer, 2009; Williams et al., 2013).

3.7 Conclusion

This is the first comprehensive systematic review of the literature, specifically examining the effects of long-term prescribed opioids on the HPG axis in women

aged 18-55 years old. This review supports the view that long-term use of opioids might have a negative effect on women's HPG axis, leading potentially to sexual and reproductive dysfunction. There is weak evidence that this may not be a class effect, and certain types of opioid or methods of delivery may have a different magnitude of effect, or none at all. The evidence found appears to show women treated with opioids have low-normal, or low levels of sex hormones, and that there are clinically significant changes including decreased libido and irregular menstrual cycle. Further work needs to be undertaken to account for CNCP, and whether this is a contributing factor to the changes noticed. The route of opioid administration, as well as type of drug and morphine equivalent dose, also needs to be investigated and whether this has any effect on the likelihood of developing hypogonadism. It might be that transdermal opioids do not cause this adverse effect, and therefore may potentially be a safer mode of opioid delivery in premenopausal women. The key to further research will be larger numbers of patients and controls who are matched for CNCP and longer follow-up periods.

4 Methodology

4.1 Introduction

This focus of this thesis is the epidemiological study of reproductive and sexual dysfunction in women who have been prescribed opioids for CNCP. This chapter describes the underpinning research methods and the study designs used to investigate the specific objectives of the thesis.

The chapter initially defines epidemiology, its uses within medical research, and its core concepts and measurements. The chapter then gives an overview of the approaches that were used to investigate opioid use, and any associated reproductive and sexual dysfunction. The strengths and weaknesses of the two core methods (cross-sectional postal survey and primary care database cohort study) used within the thesis are discussed. This chapter will also discuss some of the underlying concepts, and where problems can arise with epidemiological research (including bias, validity, reliability and confounding). The issue of health literacy will be introduced as this has a direct impact on the use of postal survey methods.

4.2 Epidemiology

Epidemiology is a word developed from Greek and when translated literally, it means “studies upon people” (Blumenthal *et al.*, 2001, p135). Epidemiology has been defined as “the study of distribution and determinants of illness and disease in populations” (Croft et al. 2010, p3). Epidemiological research can provide descriptions of a particular disease profile within a population, or look at possible causes for certain conditions by comparing different population groups (Blumenthal et al., 2001; Bowling, 2014a; Coggon et al., 2003). Epidemiological research studies

what is already happening in a population and provides evidence that relates to populations rather than individuals. The key for all epidemiological research, is to have a robust way of identifying those with and without the outcome or disease under investigation, and if necessary the exposure of interest. Epidemiology can be divided into descriptive epidemiology and analytical epidemiology. Descriptive epidemiology measures disease frequency and develops hypotheses. Analytical epidemiology investigates hypotheses and evaluates causal relationships through comparisons between different populations. This thesis focuses on the pharmacoepidemiology of opioid analgesics. Pharmacoepidemiology is specifically focused on studying the effects of medicines in populations, and is useful for investigating possible harms of medicines already in use, in particular where there is little evidence available already (Evans, 2012). Pharmacoepidemiological research into long-term opioid use is important, as there is evidence for significant risk of adverse effects with opioids, and little evidence for effectiveness of long-term opioid use in CNCP (Bedson et al., 2019a; Els et al., 2017b, 2017a). A recent overview of Cochrane reviews of adverse effects in medium and long-term opioids found no previous Cochrane reviews investigating hypogonadism as a potential adverse effect in women receiving long-term opioids for CNCP, and this has been highlighted as an area that needs further research (see the results of the systematic review discussed in Chapter 3 and background in Chapter 2 for further information) (Els et al., 2017b). Further investigation in this area will enhance the evidence base for long-term opioid use, and subsequently help to guide management decisions for long-term analgesia.

4.3 Descriptive epidemiology

Descriptive epidemiology can be defined as “the study of variations in measures of population health by time, person and place” (Bruce, Pope and Stanistreet, 2008, p38). Studies undertaking descriptive epidemiology often use routinely collected data (e.g. primary care databases and disease registers), in order to understand the distribution of disease within a population and to develop hypotheses for further investigation. The main methods for descriptive epidemiological studies are case reports, case series, cross-sectional studies and ecological studies. One of the studies in this thesis is a cross-sectional survey and its main aim is to describe the prevalence of sexual dysfunction in opioid users. Therefore, this method is discussed in more detail in section 4.4. The cohort study undertaken within this thesis uses a primary care database as its data source, and the cohort will initially be evaluated using descriptive epidemiology.

4.3.1 Measures of the frequency of reproductive dysfunction in opioid users

It is important to measure the frequency of reproductive dysfunction in opioid users in different groups, (e.g. by dose, current (vs previous) usage or duration of usage) and their data can then help to develop hypotheses regarding the potential relationship between opioids and sexual and reproductive dysfunction to be developed. The two main measures of disease frequency used in epidemiology are incidence and prevalence (the formulas for calculating these are shown in Figure 4-1). Incidence is defined as the number of new cases within a population during a specified time period (Coggon et al., 2003). Prevalence can either be the proportion of current cases at a specific point in time (point prevalence) or during a specified time period (period prevalence) within a population (Bowling, 2014a; Coggon et al., 2003).

Figure 4-1 Incidence and prevalence equations (Stewart, 2010)

$$Incidence\ rate = \frac{number\ of\ new\ cases\ in\ a\ given\ time\ period}{person - years\ at\ risk\ during\ the\ same\ time\ period}$$

$$Prevalence = \frac{number\ of\ cases\ in\ the\ population\ at\ a\ given\ time}{total\ population\ at\ the\ same\ time}$$

The gold standard for calculating an incidence rate uses person-years at risk to calculate the total population at risk during a specific time period (this takes into account the differing amounts of time that individuals contribute to a study) (Stewart, 2010). Within the cohort study undertaken within this thesis, incidence rate will be calculated as cases per person-years, this is possible as there is data for each participant from entry to the cohort until the participant leaves the cohort. The cross-sectional study will report prevalence rather than incidence as it provides data on a cross-section in time (the tools within the questionnaire refer to a period of time up to six months).

4.4 Cross-sectional studies

Cross-sectional studies are observational studies that collect data on exposure and outcomes of interest at a single time point (or time period), and provide descriptive data (Blumenthal et al., 2001; Bowling, 2014b). They are an efficient way to estimate prevalence in a population. Cross-sectional studies can either be done through collecting new data (often in the form of a postal questionnaire), or through accessing already available data, for instance from a primary care database (Berger et al., 2009). In this thesis, a cross-sectional postal survey was chosen to investigate the relationship between opioids and sexual dysfunction since it allowed women to be directly questioned with regards to their sexual function, and additionally this is an

area where using existing records may not be appropriate (Montgomery, 2008). Existing medical records may be incomplete concerning sexual dysfunction. Both clinicians and patients can find sexual function a difficult area to discuss, and there is evidence that patients will not disclose sexual problems unless they are explicitly asked due to their private and potentially embarrassing nature (Humphery and Nazareth, 2001; Montgomery, 2008)

Information from cross-sectional studies is only analysed at a single time point (or period of time), therefore temporal relationships are difficult to establish. Any relationship found is considered an association or correlation, and results must be interpreted with caution (Berger et al., 2009; Bowling, 2014b; Coggon et al., 2003; Sedgwick, 2014). If it is important to establish a temporal relationship then other study designs should be considered, for example longitudinal studies (Berger et al., 2009; Stewart, 2010). When designing a cross-sectional study it is important to take into account the need to collect sufficient data on confounding factors (see 4.7.3 for further information on confounding) so that they can be included in any statistical analysis (Blumenthal et al., 2001).

4.4.1 Measures of association in cross-sectional studies

As well as providing descriptive results, cross-sectional studies can be used to produce measures of association using odds ratios (OR) or relative risks (RR) (Reichenheim and Coutinho, 2010). OR are closely related to and often confused with RR. RR is the ratio of the disease rate in exposed participants compared to unexposed participants, RR will be discussed fully in section 4.5.1 (see Figure 4-2 for the equation which derives an odds ratio). An OR is the ratio of the odds of disease in exposed participants divided by the odds in unexposed participants, so in the case

of this thesis the odds of reproductive and sexual dysfunction in different types of opioid users (Coggon et al., 2003). The higher the denominator and the less frequent the outcome, the closer the OR approximates to RR. However, the OR overestimates the RR, particularly with small sample sizes (Coggon et al., 2003; Knol et al., 2012; Nemes et al., 2009).

Figure 4-2 2 x 2 table and equations for odds ratio

Risk Factor	Disease	No Disease	Total
Present	a	b	a + b
Absent	c	d	c + d
Total	a + c	b + d	a + b + c + d

$$Odds\ Ratio = \frac{a/b}{c/d}$$

Logistic regression can be used to model a relationship between an exposure and outcome and produces an odds ratio. This describes the relationship between an independent variable and a dichotomous outcome (such as in this study where reproductive dysfunction is either present or absent). Logistic regression can either be univariate or multivariate (Tripepi et al., 2008). When using logistic regression to model odds ratios in cross-sectional studies, certain assumptions should be met in the data if the aim is to investigate any causal relationship. First, the population should be steady (in cross-sectional studies there is a population at a single point/period in time so it will not change, but in other studies the population should be

the same at the start as at the end of the study period). Second, there should be no reverse causality (sexual dysfunction would never be an indication for opioid use). Third, exposure must precede the outcome, and finally, duration of the outcome must be the same across groups. If these are all met, then logistic regression is an appropriate measure for cross-sectional studies (Reichenheim and Coutinho, 2010).

Univariate logistic regression takes the likelihood (probability of the outcome occurring/1-probability of the outcome occurring) of a dichotomous outcome based on a descriptive factor (in the case of the cross-sectional study sexual dysfunction and opioid use respectively) and then transforms this using a natural logarithm. This logarithmic transformation produces a linear relationship, which is then used in regression analysis in order to predict how the log (odds) of the outcome changes based on independent variables. Figure 4-1 shows how univariate logistic regression is calculated, logit y is the natural logarithm of the likelihood, β_0 is the value of logit y when the independent variable is 0, x represents the independent variable and β_1 is the estimated regression coefficient for the independent variable. This regression coefficient indicates the expected change in the log of the odds for a single unit increase of x (for instance the increase of the log of the odds of sexual dysfunction for an increase for one year in age). To get the final OR from univariate logistic regression, the value for β_1 is exponentiated using the natural logarithm. The OR is the odds of the outcome occurring or not based on a single unit increase in the descriptive factors (Sullivan, 2013; Tripepi et al., 2008).

Figure 4-3 Equations for univariate and multivariate logistic regression.

Univariate analysis

$$logit\ y = \ \beta_0 + \ \beta_1 xy\ (likelihood\ of\ the\ outcome)$$

$$= \frac{probabilty\ of\ the\ outcome\ occuring}{1 - probability\ of\ the\ outcome\ occuring}$$

$$odds\ ratio = \ e^{\beta_1} = 2.1783^{\beta_1}$$

Multivariate analysis

$$logit\ y = \ \beta_0 + \ \beta_1 x_1 + \ \beta_2 x_2 + \cdots + \ \beta_n x_n$$

Key: β_0 represents the value for logit y when the independent variable is 0, X represents the independent variable, $\beta_1$represents the regression coefficient and e represents the value for the natural logarithm (2.1783). Adapted from (Tripepi et al., 2008).

Multivariate logistic regression is possible due to the conversion of the dichotomous outcome to a linear relationship, and therefore multiple independent risk factors can be included in a single model. This means that the effect of the independent factor, in this case opioid use, can be adjusted for multiple other factors including confounders, for instance in the cross-sectional study age and pain status. The equation for multiple logistic regression is shown in Figure 4-3 as it is an extension of univariate analysis, where multiple independent variables (x_n) are included in the model to predict the likelihood of the outcome. When undertaking multiple logistic regression, β_n represent the changes in the expected odds with a one unit change of x_n, when all other variables are held constant. In multiple logistic regression it is important that independent variables are only included within the model if there is clinical reasoning to suspect that they can affect the dependent outcome.

OR and multiple logistic regression will be used within the cross-sectional element of the thesis to assess the measure of association between opioid use and sexual dysfunction and this will allow for adjustment for confounding factors.

4.4.2 Cross-sectional postal surveys

Cross-sectional postal surveys are considered quick and relatively inexpensive to undertake. Additionally, it is possible to cover a widely distributed population (Kelley et al., 2003; Mann, 2003). If an appropriate sampling frame for the population is selected, then it is reasonably easy to select a representative sample, and providing non-response is not an issue (either very good response rate or no difference between responders and non-responders) the results can be generalisable to the population of interest (Kelley et al., 2003). The sampling frame for the cross-sectional study within this thesis will be GP patient lists within the West Midlands Clinical Research Network (WM:CRN) (WM:CRN, 2019). The cross-sectional study investigates women prescribed opioids, of whom all should be registered at a GP practice as otherwise they would be unable to access prescribed medicines. It is therefore an appropriate sampling frame (Herrett et al., 2015). The information gained from a postal survey, has the advantage that it can be tailored in order that the investigator can ask everything they believe will be required for analysis, but this may not be the case for secondary data (Stewart, 2010). Bias can occur with survey research if there are problems during data collection (Delgado-Rodriguez and Llorca, 2004). There are many different types of bias including misclassification bias, observer/interviewer bias, social desirability bias and recall bias. Misclassification bias is when cases or those exposed can be misclassified as being controls or unexposed or vice versa. Most studies have an element of misclassification bias, and

it is particularly important when this bias is not independent of the identification exposure and outcome and therefore different between comparison groups as this can then affect any association seen during analysis (Delgado-Rodriguez and Llorca, 2004). Postal questionnaires, when compared to face to face interviews, minimise social desirability bias (the phenomenon where the person answering questions does so based on what they assume is the correct answer, or on what they feel will make them appear in the best light). However social desirability remains an important issue for all self-report measures (Bowling, 2005, 2014c). There are several ways to combat social desirability bias within a postal questionnaire, one of the most common methods is the use of scales with several questions rather than single items. These tools can then be analysed for internal consistency (see section 4.4.4 for further details). Postal questionnaires offer more anonymity than face-to-face or telephone interviews, so are useful when investigating sensitive subjects. This is particularly important for this thesis as the main outcome for the cross-sectional study is sexual dysfunction, which may be considered a sensitive subject (Stewart, 2010; Tourangeau and Yan, 2007). Postal surveys are not subject to observer/interviewer bias (where the knowledge of the disease or exposure status can influence the data being recorded) (Delgado-Rodriguez and Llorca, 2004; Stewart, 2010). Recall bias is a particular type of information bias where those taking part in the study with either the disease or the exposure of interest, are more prone to recall either the consequences of a possible exposure or the exposure itself (Blumenthal et al., 2001; Stewart, 2010).

One of the disadvantages of postal surveys is non-response, this needs to be taken into account following a sample size calculation in order to ensure enough

questionnaires are disseminated to achieve the required sample size (Kelley et al., 2003). Non-response decreases the effective sample size and can introduce non-response bias, if those who do not respond are systematically different from those who do respond, and this systematic difference is related to the factors of interest for the study. This is discussed fully in 4.7.1 (Bowling, 2014b; Delgado-Rodriguez and Llorca, 2004). Investigating sensitive subjects can mean that there is higher non-response (of the entire questionnaire and of individual questions considered to be sensitive), and measurement error through participant misreporting (answering untruthfully either consciously or subconsciously) than with non-sensitive questions (Stewart, 2010; Tourangeau and Yan, 2007).

When postal surveys are sent, they rely on the study population being literate and able to speak a common language, and they are only suitable if the questions are straight forward and easy to understand (Bowling, 2014c). Survey research is complex and it is often difficult to perfect question wording, form and order, all of which can affect the responses obtained, as well as the overall formatting of the survey (Bowling, 2014c). As postal surveys rely on structured questionnaires, a respondent may feel that their answer does not fully fit one of the responses and this may lead to either item non-response, or the respondent selecting more than one answer (Bowling, 2014d). Additionally, as surveys often do not allow free text responses, this can mean there can be a lack of depth in information. However, this is not necessarily a problem if this information is not required for analysis (Kelley et al., 2003). As postal surveys arrive at a household there is no way to control who actually completes the survey, or be sure that there have been no external influences on the respondent completing it (Bowling, 2014c).

Information bias is when important information is either collected, interpreted or measured incorrectly and results in misclassification of the participant either for the exposure or outcome. Information bias can occur when the respondent is trying to complete a questionnaire quickly or has little interest in the subject. This can affect responses in several ways, for instance the participant may neither agree nor disagree with a statement, choose the same answer for all the questions, or mentally flip a coin in order to pick an answer, this is known as satisficing (Streiner et al., 2014). Methods to avoid satisficing include ensuring questions are as simple and relevant as possible in order to maintain the respondents motivation (Streiner et al., 2014).

Protopathic bias is another form bias, where the exposure is related to early signs of the disease under investigation, and so results may reflect the natural course of the disease. Pain is often an early sign of many conditions and quite naturally, analgesics are therefore often prescribed or purchased over the counter. The disease of interest will progress over its natural course, and the analgesics could then be considered a risk factor, when in fact they were prescribed for the early stages of the condition. However this is unlikely to be the case in the cohort study, as pain is not considered an early symptom of any of the outcomes included within the study, although it is possible that CNCP may be related to symptoms of low libido (Ambler et al., 2001; Delgado-Rodriguez and Llorca, 2004; Signorello et al., 2002).

See Table 4-1 for a summary of the advantages and disadvantages of postal cross-sectional surveys.

Table 4-1 Advantages and disadvantages of postal and cross-sectional surveys

Postal cross-sectional surveys	
Advantages	Disadvantages
Postal surveys	
1. Quick and low-cost 2. Avoids interviewer bias 3. Minimises social desirability bias 4. Useful for investigating sensitive subjects 5. Investigation of multiple exposures and outcomes possible	1. Respondent may misunderstand a question and there is no way to know whether this has occurred 2. Non-response bias a. Unit non-response b. Item non-response 3. Reliance on closed questions 4. Must be as short as possible 5. No control over who completes survey 6. Population of interest must be literate and speak a common language 7. Recall bias
Cross-sectional studies	
1. No loss to follow-up	2. Single time point

4.4.3 Validity and postal surveys

Validity is the extent to which a concept is accurately measured and how well the conclusion drawn reflects the real situation in the population studied (Heale and Twycross, 2015). Validity can be split into two core concepts: external and internal validity. External validity is the ability to generalise the study findings to the population of interest. Internal validity is both the ability of the study to accurately identify the outcome of interest and classify the exposure, and then to correctly characterise the relationship between the exposure and outcome (Bowling, 2014e; Campbell, 1957; Coggon et al., 2003; Delgado-Rodriguez and Llorca, 2004). These concepts are important in all epidemiological research and need to be considered during the design phase of any study.

External validity

External validity can be threatened by selection bias, where the characteristics of the sample included in the study differ from those of the population of interest, and therefore the sample does not represent the target population (Bowling, 2014e; Delgado-Rodriguez and Llorca, 2004). Selection bias can occur for many reasons including ascertainment bias where the cases selected do not represent the cases in the population, sampling bias where the way the population is sampled introduces bias, and bias introduced through loss to follow-up or non-response (see section 4.7.1 for further detail) (Delgado-Rodriguez and Llorca, 2004). Another way in which selection bias can be introduced is when the initial identification of those included in the study is related to the factor being studied (Blumenthal et al., 2001; Delgado-Rodriguez and Llorca, 2004; Kelley et al., 2003).

The initial sampling frame is important in order to ensure the population of interest for the study is represented. GP registers are a comprehensive sampling frame within the UK, and they provide almost universal coverage (over 98%) of the population and GPs provide the vast majority (over 90%) of patient contacts within the NHS (Gregory, 2009; Herrett et al., 2015). However, it is important to remember that in the case of the cross-sectional study, only those practices that wish to take part will be included, and this may not be representative of the whole UK population, but will be representative of the local population. However, there are certain groups that are more likely to be absent from these lists: prisoners, asylum seekers, travellers and the homeless (Hall et al., 2012). In the case of the cross-sectional study described in this thesis, the population of interest is women 18-45 years of age receiving prescribed opioids for CNCP, so using a primary care sampling frame is likely to accurately represent this population. There are many types of sampling but the two main types are random sampling and non-random sampling (Kelley et al., 2003). Sampling error is the probability that a sample is not representative of the population from which it has been drawn. Simple random sampling will give the closest estimate of the population than any other sampling methods (Berg, 2005; Kelley et al., 2003). Selection bias due to sampling bias can occur when non random sampling is undertaken and this may mean that the comparison groups are systematically different to one another (Delgado-Rodriguez and Llorca, 2004; Stewart, 2010). Both the studies within this thesis use primary care lists as sampling frames. The cohort study uses the clinical practice research datalink (CPRD) and the cross-sectional study uses GP registers from within the WM:CRN. Any woman identified through initial searches as meeting the inclusion criteria will be included in the study, so no

sampling bias will occur following identification based on the inclusion and exclusion criteria (which will be described in detail in the relevant methods sections).

Loss to follow-up is a form of selection bias in longitudinal studies where those that start the study do not contribute data until the end because they have, for whatever reason, stopped responding (Kristman et al., 2016). Loss to follow-up in the cohort study undertaken for the thesis only occurs if the patient dies or leaves the contributing general practice. These two groups may be older (the cohort only included 18-55 year olds) or have moved location more often than other patients and this could potentially affect the results. Selection bias is minimised in both studies undertaken within the thesis, as they each take complete samples identified through primary care registers, which are appropriate sampling frames for the populations of interest. Loss to follow-up should not occur in either study as the cross-sectional study is only examining a single point in time and the cohort study uses retrospective data.

Internal validity

Internal validity was defined previously within this section. It describes whether the study accurately identifies the outcome of interest and the relationship between the exposure and outcome (Bowling, 2014e; Campbell, 1957; Coggon et al., 2003; Delgado-Rodriguez and Llorca, 2004). This is particularly important in studies using surveys to identify the outcomes of interest, so in this thesis is relevant to the cross-sectional postal survey. Face validity is where the study investigator makes an assessment at face value about whether the questions appear to be relevant, reasonable, unambiguous and clear (Bowling, 2014e). A more systematic way of measuring this is to assess content validity, which is similar to face validity, but

usually involves a panel making judgments about whether the full spectrum of a condition is covered by the tool (Bowling, 2014e; Heale and Twycross, 2015). Construct validity assesses whether the instrument measures the intended concept and can be split into convergent validity where the tool should correlate with similar variables, and discriminant validity where the results should not correlate with dissimilar tools (Bowling, 2014e; Heale and Twycross, 2015). Criterion validity is the extent to which a research instrument is comparable to other instruments that measure the same variable and ideally any new instrument would be compared to the gold standard or the closest alternative if this is not available (Bowling, 2014e; Heale and Twycross, 2015). The cross-sectional study will use previously validated items where possible. This is particularly important for the identification of the exposure and outcomes, as identifying these correctly is important for internal validity.

4.4.4 Reliability and postal surveys

Reliability is the accuracy and consistency of a research instrument (Heale and Twycross, 2015; Tavakol and Dennick, 2011). Reliability is important for postal surveys as it helps to ensure that the results are reproducible, and that all the items are measuring the same concept. There are many ways to test reliability; the most common way of doing this is through the use of Cronbach's alpha, a test to determine the internal consistency of an instrument. Internal consistency is the extent to which all the items within a tool measure the same concept or construct. Cronbach's alpha can only be used if there are more than two items in a tool and it produces a result between zero and one. The higher the result the more reliable the test is. An acceptable reliability score is ≥ 0.7. However values >0.9 may indicate that

some questions could be removed as there may be some redundant items (for instance where more than one item is measuring the same aspect and a single item would provide the same level of information) and this could decrease the length of the tool (Heale and Twycross, 2015; Tavakol and Dennick, 2011). It is important to remember that if a tool includes sections for different constructs or conditions, then Cronbach's alpha should be calculated for each section individually. Cronbach's alpha will also be affected by the length of the tool and the longer the tool is, the higher the alpha result will be (likely due to similar questions causing redundant items as explained above). Cronbach's alpha is a measurement of reliability for the whole tool (Tavakol and Dennick, 2011). When selecting tools for inclusion in the postal survey the reported reliability will be considered during the assessment process.

4.4.5 Health literacy and postal surveys

Health literacy has been defined as "the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good health" (Nutbeam et al. 1998, p357). Health literacy is a particularly important concept for the cross-sectional survey as it directly influences the participants' ability to understand and answer the questions. For instance, the questionnaire for the cross-sectional study relies on patients understanding which medicines they are using for pain relief. There are different skills that contribute to health literacy. These are functional health literacy, interactive health literacy and critical health literacy (Rowlands et al., 2014). In the context of a postal survey the most important skill is functional health literacy, which is the ability of a person to read and understand information in front of them since if the question is not understood, it may lead to item non-response (Paz et al., 2009;

Rowlands et al., 2014, 2015). The validity of data collected from self-report is dependent on the respondents ability to understand each survey item, which is a direct reflection of their functional health literacy (Paz et al., 2009). The more difficult a question is to understand the higher the likelihood of non-response (Paz et al., 2009). Interactive health literacy and critical health literacy are less important for the study, as these revolve around discussions with health professionals and patients taking control of their own health (including asking questions when discussing new medicines leading to better shared decision making and taking positive action to change their environment and how this can affect their overall health) (Rowlands et al., 2014).

The Organisation for Economic Co-operation and Development (OECD) studied adult skills (to assess skill levels to see how these match with the demands of the workplace) and found that 16.4% of adults (aged 16-65 years old) in the UK had a literacy level at or below level one (the equivalent to a D-G grade at GCSE (General Certificate of Secondary Education), the grade range for GCSE's is A-F, indicating these adults would achieve a low level pass at GCSE) (OECD, 2012). Adults reading at level one, would typically be able to understand information about familiar topics, and be able to find a single piece of information from the text, the level expected from eight to ten year olds (OECD, 2012). Low literacy is associated with lower socioeconomic status and poor health (OECD, 2012; Paz et al., 2009). A study specifically looking at health literacy in the UK, found that 43% of those studied fell below the competency threshold for understanding text in 64 patient information leaflets (for various conditions and treatments) (Rowlands et al., 2015). Health literature is an area where there appears to be a great discrepancy between the

reading level of those it is aimed at, and the complexity of the writing (Meade and Smith, 1991; Rowlands et al., 2015). It is therefore prudent when designing self-completion surveys to aim for a reading level of around 8-10 years old, or five years of formal education. This needs to include patient information leaflets and consent forms which are particularly important since they are only valid if the participant has been fully informed, and was therefore able to make a decision to participate based on this information (Health Research Authority, 2017).

Tools for assessing reading level of texts

There are several commonly used tools for assessing the readability of a text, some of the most commonly used are the Flesch-Kincaid, The Simple Measure of Gobbledygook (SMOG) and Flesch reading ease tools (Calderón et al., 2006; McLaughlin, 1969; Meade and Smith, 1991; Paz et al., 2009; Wang et al., 2013). These tools use formulas including factors, such as the number of syllables per word and words per sentence to calculate a reading grade, the formulas for each tool are shown in Table 4-2 (Wang et al., 2013). However, these tools do not take into account the structure of the sentence or context and therefore are a slightly simplistic way of assessing the reading ease of a passage of text (Meade and Smith, 1991). The tools also do not assess whether words are easily misunderstood in the context, for instance the word chronic which is commonly used by health care professionals to mean a long-term illness but may be understood by patients to mean a severe illness (Rowlands et al., 2014). The tools can be very variable and will often give very different reading ages to each other. This is due to the fact that the tests are looking for a different level of comprehension, with SMOG aiming for people to understand 100% of the text compared with only 35% understanding for Flesch-Kincaid (Meade

and Smith, 1991; Wang et al., 2013). Flesch and Flesch-Kincaid are commonly used, as they are included as part of Microsoft Word packages, and this facilitates their ease of use (Microsoft, 2013a). These tools integrated into Word will be used to assess the patient facing materials used within the cross-sectional study and where possible steps will be taken to reduce the reading age.

Table 4-2 Commonly used readability tools (Calderón et al., 2006)

Tool	Formula	Outcome	Comprehension
Flesch-Kincaid	$= (0.39 \times Average\ Sentence\ Length) - (84.6 \times Average\ number\ of\ syllables\ per\ word)$	Grade levels 5th to College graduate	35%
SMOG	$= 3 + \sqrt{number\ of\ words\ with\ \geq 3\ syllables} \times \frac{30}{number\ of\ sentences}$	Grade levels	100%
Flesch	$= 206.835 - (1.015 \times average\ sentence\ length - (84.6 \times average\ number\ of\ syllables\ per\ word)$	0-100. Higher score indicates easier readability	75%

4.5 Analytical epidemiology

Analytic epidemiology involves investigating hypotheses in order to understand possible causal relationships (Bruce et al., 2008). Analytical epidemiology is most often undertaken in case-control studies and cohort studies. One of the focuses of

this thesis will be to investigate the relationship between opioid use and reproductive dysfunction through a retrospective primary care database cohort study. One of the most important steps during the design stage of any study is a sample size calculation. Sample size calculations are based on the power (the probability of detecting an effect, given that the effect is really there) required (usually greater than 0.8), the significance level that will be used (usually a P value of 0.05) and the predicted difference between the two groups (Bowling, 2014a).

4.5.1 Measures of association in analytical epidemiology

Prior to undertaking an analytical study and tests of statistical significance, it is important for the researcher to have developed a research question and an associated null hypothesis. A null hypothesis is the assumption that there will be no association or effect (an effect size equal to zero) and when it is rejected an association or effect is shown to be possible (Greenland et al., 2016). In the case of the cohort study within this thesis, the null hypothesis is:

There is no difference in reproductive dysfunction between those prescribed opioids dependent on duration of use (long-term vs short-term).

The null hypothesis is used as the basis for testing the data and if it is rejected the alternative hypothesis is accepted - in this case, that there is a relationship between opioid use and reproductive dysfunction. In epidemiological work it is important to assess the probability that any observed relationship has occurred by chance, or is due to other factors (such as other exposures or confounding factors) (Wassertheil-Smoller, 2004). Statistical tests can be either one or two sided. Two-sided tests, test for both directions of change (either an increase or decrease in the study population

compared with controls) whereas a one sided test will only test one direction (either that the exposure is more or less likely to cause the outcome). In this thesis, two sided tests will be used as the null hypothesis expects no difference between groups. Analytical tests return probabilities (P values); the lower the P value the more likely the null hypothesis is incorrect. The level at which the null hypothesis is rejected is conventionally taken to be (and throughout this thesis) as ≤0.05. The level at which the P value is considered significant (alpha α) should be decided during the design phase (Greenland et al., 2016). It is important to remember that the calculation of probability relies on all the assumptions underlying the model being true, in order to test the null hypothesis (for instance random sampling of those included) (Greenland et al., 2016).

Confidence Intervals (CI) are useful for interpreting statistical significance of a test. The benefit is that they provide a range for the likely value, whereas a P value indicates the probability of the observed value occurring by chance. P values and CI (most commonly a 95% CI is used) are however closely interlinked, and it is recommended that P values are not interpreted in isolation (Greenland et al., 2016). The 95% CI indicates that if the same investigation was undertaken and sampled in the same way, 95% of times the true value for the population mean will be found within this range. As such the 95% CI reflects how precise the results are (see Figure 4-4 for the equation for a 95% CI) (Blumenthal et al., 2001; Greenland et al., 2016; Stewart, 2010). The larger the sample size, the narrower the 95% CI is likely to be and, as long as the sample was appropriate, the closer the sample mean is likely to be to the population mean (Stewart, 2010). 95% CI will be used throughout the thesis

where appropriate to indicate the precision of the estimate, and whether it might be considered a significant result.

Figure 4-4 How to calculate 95% confidence interval (Stewart, 2010)

$$95\%\ Confidence\ Interval = Sample\ mean\ \pm (1.96\ \times standard\ error)$$

$$Standard\ error = Standard\ Deviation \div (\sqrt{sample}\ size)$$

As discussed previously with OR in section 4.4, epidemiologists can also undertake calculations to estimate risk and whether there is a link between an exposure of interest and the incidence or prevalence of a disease (measures of association) (Wassertheil-Smoller, 2004). There are many ways to calculate the risk of an outcome (dependent on the study design), these include relative risk, attributable risk (the risk difference between exposed and unexposed people) and population attributable risk (the risk difference between the total population and the exposed population and indicates the reduction in incidence if the exposure was completely removed) (Stewart, 2010; Wassertheil-Smoller, 2004). Relative Risk (RR) is the ratio of the disease rate in exposed participants when compared to unexposed participants (see Figure 4-5 for the equation to calculate relative risk). A RR of one indicates no risk associated with the exposure of interest, a RR greater than one indicates an increased risk and less than one a decreased risk (Coggon et al., 2003; Stewart, 2010). RR will not be used during this thesis. OR is more appropriate for the cross-sectional study, as it can be adjusted for confounding factors using multiple logistic regression within the available statistical software packages, and Cox regression which estimates hazard ratios (discussed fully later in this section) is more appropriate for the cohort study.

Figure 4-5 Equations for calculating relative risk based on a 2 x 2 table

$$Relative\ Risk = \frac{a/(a+b)}{c/(c+d)}$$

Chi-squared analysis is used to compare observed categorical variables to those expected in the population based on 2x2 tables see Figure 4-2. Expected values are calculated and compared to the actual values by the chi-squared calculation (in normal practice a Yates correction is used on the formula) (Figure 4-6), the chi-squared value is compared with the known distribution of chi-squared to give the likelihood of the difference occurring by chance (Wassertheil-Smoller, 2004). Chi-squared analysis is used during the thesis to compare distributions of descriptive and explanatory variables between the different exposure groups.

Figure 4-6 Chi-squared formula and chi-squared with Yates correction. O=observed, E=expected and lower case letters indicate boxes in a 2x2 table. Taken from (Wassertheil-Smoller, 2004).

$$Chi-squared = \frac{(Oa-Ea)^2}{Ea} + \frac{(Ob-Eb)^2}{Eb} + \frac{(Oc-Ec)^2}{Ec} + \frac{(Od-Ed)^2}{Ed}$$

$$Chi-squared\ with\ Yates\ correction = \frac{N\left(|ad-bc| - \frac{N}{2}\right)^2}{(a+b)(c+d)(a+c)(b+d)}$$

The cohort study undertaken for this thesis will use survival analysis, as it is able to examine the effect of an exposure, taking time into account (Bradburn et al., 2003a). The most common way of undertaking multivariable analysis of survival time is the Cox proportional hazards model (Bradburn et al., 2003a). The Cox proportional hazards model is semi-parametric, and it models the effect of predictors and covariates on the hazard rate but leaves the baseline hazard rate unspecified. It does

not assume knowledge of absolute risk estimates, but does rely on the assumption of proportional hazards (where the factors included in the model have a constant effect over time) (Cox, 1972). Hazard is the probability that an individual within the study at time (t) will have an event at that time (Clark et al., 2003). Analysis accommodates for censored subjects (a participant is censored if an outcome of interest occurs, an unrelated death occurs, or the patient is lost to follow-up). This is important when undertaking database research, as participants may leave a contributing practice at any time. In Cox regression, the dependent variable is the hazard function at any given time, it does not assume that survival follows a particular distribution which is an advantage when compared with other forms of survival analysis (Bradburn et al., 2003a). For survival analysis to be valid, there needs to be a minimum of 10 events for each covariate included in the model. Less than this and results should be interpreted with caution (Peduzzi et al., 1995). Multivariable models are useful when a single exposure or risk factor is being studied but several other risk factors exist and these need to be adjusted for during analysis, when building a model it is important to consider both the statistical and clinical importance of possible covariates and confounders (Bradburn et al., 2003b). Cox regression relies on the assumption of a constant relationship between the dependent variable and the explanatory variable. This assumption can and should be tested through use of Kaplan-Meier graphs, log-log plots and Schoenfeld residuals (a statistical test for the association between residuals and time; if $p < 0.05$ it indicates that the proportional hazards assumption does not hold), and this assumption is more likely to be violated if follow-up periods are long (Bellera et al., 2010; Bradburn et al., 2003b). If the proportional hazards assumption is violated for certain covariates, they may still be included within the model but as time varying covariates (tvc). This takes into account

the covariate interacting with log (time), so they are modelled as covariates that alter over time (Bradburn et al., 2003b). All variables to be included in the models within this thesis will be tested prior to inclusion, and if they violate the proportional hazards assumption then they will be included as time varying covariates as described above.

4.6 Cohort studies

Cohort studies follow two or more groups (exposed group compared to a non-exposed group) from exposure (or prior to exposure) to outcome (Blumenthal et al., 2001; Stewart, 2010). Cohort studies can either be prospective (where participants are followed from exposure forwards through time) or retrospective (where the groups are identified in the past then followed through to the present) (Stewart, 2010). It is important that the comparison groups are as similar as possible in all ways except for the exposure of interest, to decrease confounding (Grimes and Schulz, 2002). Cohort studies are useful when temporal relationships between exposure and outcomes are being studied (Berger et al., 2009). Loss to follow-up is a problem in prospective cohort studies, as they can run for very long periods of time, and loss to follow-up needs to be taken into account during the design process. Retrospective cohort studies do not suffer from loss to follow-up but missing data can be a problem, as data was initially collected for a different purpose (Stewart, 2010). Using RR is the preferred method of assessing the likelihood of exposed people developing the disease when compared to the unexposed participants, however this does not take into account the role of time. If it is important to include time within the analysis then Cox regression can be used, this produces a hazard ratio and was used for the cohort study undertaken for this thesis (see section 4.5.1 for further details) (Cox, 1972; Stewart, 2010).

A database cohort study was chosen as the method for the first study included in this thesis. It provides an efficient way to examine a large number of women to assess for a possible relationship between opioid use and reproductive and sexual dysfunction.

4.6.1 GP consultation database research

Database research uses routinely collected data in order to answer research questions. These types of databases are often known as multi-purpose databases (Hall et al., 2012). Within the UK there are many longitudinal primary care databases that can provide anonymised patient records for research. These include ResearchOne, CALIBER (Clinical research using LInked Bespoke studies and Electronic health Records), The Health Improvement Network (THIN), QResearch and Clinical Practice Research Datalink (CPRD) (Vezyridis and Timmons, 2016). UK healthcare is uniquely positioned to provide almost complete population coverage through primary care databases, thanks to the NHS providing almost universal healthcare. There are more than 9000 general practices in the UK and each database receives data from only a small fraction of these (NHS Information Centre for Health and Social Care, 2012). Research using primary care databases has grown considerably over the last decade. A systematic review of publications using CPRD, THIN and QResearch found an increase from seven papers published in 1995 to 171 in 2015 (Vezyridis and Timmons, 2016). The same review found that a strong focus of research within databases, seems to be drug safety research and the journal with the most publications was Pharmacoepidemiology and Drug Safety (Vezyridis and Timmons, 2016). RCTs are the gold standard for investigating the efficacy of a new medicine, however there is also a place for observational studies to investigate these medicines in everyday clinical practice (Berger et al., 2009). Based

on the recent research undertaken using primary care databases, it appears that this would be an appropriate method to investigate the pharmacoepidemiology of opioids (Vezyridis and Timmons, 2016).

Factors to consider when selecting a database include population covered, geographical location, latency of data (the delay between an event occurring and this information being included in the database), data linkage, quality and validation of data (Berger et al., 2009; Hall et al., 2012). UK databases should provide good population coverage but as discussed in section 4.4.3 they may miss some specific populations including prisoners. If these populations were required then another method with primary data collection might be more appropriate (Hall et al., 2012). Prior to accessing data, it is important to define exposure, outcome, confounders, and inclusion and exclusion criteria. The database should be checked to see if the required information is present, easily accessible and contains the appropriate level of detail, for instance antenatal care may be missing and if you are studying this particular area it may not be appropriate to use a primary care database (Hall et al., 2012). It is important to consider whether there is any bias built into the system, for instance recording of abnormal investigation results but not normal results (Hall et al., 2012). Another consideration is whether the database provides long enough follow-up after an exposure in order to observe the outcome of interest. This requires having an idea of the period of time between exposure and outcome (Hall et al., 2012).

CPRD is funded by the National Institute for Health Research (NIHR), and the MHRA and owned by the UK Department of Health. CPRD contains the records of 11 million patients (4.4 million active) from 674 general practices (Herrett et al., 2015). CPRD is

the only database accessible online, and it extracts data from multiple clinical systems, which means that any GP can contribute data (there are three main clinical systems currently in use in the UK by GPs EMIS, Vision and SystemOne). It also has permanent data linkage to secondary care through Hospital Episode Statistics (HES) (Vezyridis and Timmons, 2016; Williams et al., 2012). THIN contains data from around 600 GPs that use the Vision clinical system and has health records for 3.7 million active patients. THIN has to be accessed at source and is not available online (IMS Health Incorporated, 2015). QResearch contains health records for 18 million patients from 1000 GPs and collects data from practices that use EMIS. Access is restricted to academics employed by UK universities and this is limited to sample data sets of maximum 100000 patients (Nottingham, 2012). CPRD was chosen as it contains linked data, which was important for the cohort study, which this cohort is a secondary analysis of due to the outcomes of interest (Bedson et al., 2019a). It is also not restricted to just one GP records system. CPRD has been shown to be broadly representative of the UK population and the sub set of practices that have HES linkage are also representative. This will be discussed fully in Chapter 5 (Herrett et al., 2010, 2015; Williams et al., 2012).

Primary care database research

The advantages of primary care database research are that it allows for large sample sizes that are broadly representative of the UK population, and also provides long-term follow-up data. Primary care databases contain information on all aspects of patient care including conditions, prescriptions, lifestyle factors and secondary care contacts (Herrett et al., 2015). Data within primary care databases are recorded for clinical care, and even though this means it is not specifically collected for research,

it does mean there is a need for the primary care clinician to record quality information, as this directly affects patient care at practice level (Gnani and Majeed, 2006). Information in primary care databases is constantly updated, and this means it can be ideal for monitoring treatments and their possible adverse effects in a real world setting (Herrett et al., 2015). It is important to remember when using databases for pharmacoepidemiological research, that results can be limited by bias and confounding, and this should be taken into account when drawing conclusions. However, this is a very cost effective way to investigate prescribed medicine, and can provide a long period of follow-up in comparison with RCTs (Gnani and Majeed, 2006).

One of the disadvantages of using routinely collected primary care data is (as discussed above), that information is extracted from systems that are designed for patient care (not for research). This means it may not provide the detail or information required for the study (Gnani and Majeed, 2006). Primary care databases can have issues with missing data, for instance ethnicity and social status. Some data (e.g. BMI, Blood pressure (BP) and smoking) may be recorded more frequently in those with certain conditions (e.g. cardiovascular disease and women receiving oral contraception), as these measurements are required by the quality outcomes framework (QoF) (this is a national voluntary scheme for GPs where certain targets are set and if met the GP receives an annual reward) (National Health Service, 2017). This means that the data may be more likely to be missing not at random (MNAR, this will be explained further in section 4.7.2) (Herrett et al., 2015). Medical records may also include more information on participants who have the exposure of interest when compared to unexposed participants and this is known as recorder

bias. This may affect the cohort study, as those receiving long-term opioids compared to short-term opioids are likely to see their GP more often, and therefore potentially have more information in their records (Delgado-Rodriguez and Llorca, 2004; Stewart, 2010). Missing data can also be introduced, where conditions are self-managed at home (this could include with the use of over-the-counter medicine), or where the patient does not consider them sufficiently important or serious to discuss with their GP. This is known as the 'clinical iceberg' and only the tip of the iceberg is seen within primary care constituting the conditions that the GP is aware of (as the patient has consulted) and have been coded within the database and only prescribed medicines are included in the database (Herrett et al., 2015; Last, 1963). Missing data may also be due to the use of free text (adding information without coding), and in the majority of cases free text has not been utilised in database research in the past. Consequently some diagnoses, in particular early symptoms and signs, could be missed and potentially bias results (Price et al., 2016; Williams et al., 2012). Primary care databases are made up of GP practices that have volunteered to be included and there is evidence that these volunteer practices are often larger and provide above average quality of care, so they therefore may not be representative of all GPs (Gnani and Majeed, 2006). For a summary of the advantages and disadvantages of research using CPRD see Table 4-3.

Table 4-3 Advantages and disadvantages of CPRD database research

Primary care database research using CPRD	
Advantages	Disadvantages
1. Large sample size available 2. Anonymised records 3. Information on all aspects of medical care 4. Linkage to HES and ONS 5. Cost-effective as data collected as part of routine care 6. Longitudinal studies can be undertaken in a timely and cost-effective manner 7. Low level of biases as data is collected for routine medical care 8. Not subject to recall bias	1. Routinely collected data so database may not contain all the information required to answer the specific research question 2. Missing data, for instance BMI, and if information is recorded in the free text rather than coded 3. No data on self-managed conditions (clinical iceberg), including no information on over the counter medicine 4. Specific populations missing e.g. homeless 5. Diagnostic labels may reflect variations in individual clinician practice rather than adhering to set diagnostic criteria

4.7 Bias

Bias can be defined as “systematic error that results in an incorrect estimate of the association between exposure and disease” (Blumenthal *et al.*, 2001, p140). Bias

can be particularly important in epidemiological research and can affect the conclusions that are drawn, so it should always be considered during both design and interpretation of studies. Selection bias and information bias have been discussed previously (see Sections 4.4.2 and 4.4.3). In this section the focus will be non-response bias (a form of information bias) and the effect that this can have, including the impact of missing data.

4.7.1 Non-response bias

Non-response bias is caused when those who respond are systematically different from those who do not respond (Delgado-Rodriguez and Llorca, 2004). Non-response bias can happen in one of several ways: loss to follow-up (if this is different between the groups under study), missing information about certain variables that is different between groups under study, and non-response to the survey (Delgado-Rodriguez and Llorca, 2004). However, it is important to note that the presence of these factors does not automatically mean that bias is introduced. Non-response can be either unit or item non-response. Unit non-response occurs when the subject does not respond at all, despite being included in the study. Item non-response is where certain parts of the information requested are missing (Berg, 2005). Response rates tend to be lower for postal surveys than face-to-face or telephone interviews and when sensitive questions are included within the questionnaire (Edwards et al., 2009). Non-response is therefore particularly important for the cross-sectional survey undertaken for this thesis.

First, considering unit non-response, the amount of bias introduced by unit non-response is dependent on the level of non-response but also the difference between responders and non-responders (Fowler, 2014). There is no agreed minimum for

acceptable response rates, but it is important to try to maximise response rates and if possible it is important to have information about how responders and non-responders may differ (Berg, 2005; Fowler, 2014). Responders may not represent the study population and therefore may not be generalisable to the population of interest (Kelley et al., 2003). As part of the cross-sectional study, age and registered GP (which will give an estimation of deprivation) of responders and non-responders will be able to be compared, and this will be useful in understanding whether the two groups differ systematically.

Item non-response is where a respondent answers some, but not all of the questions in the survey (Berg, 2005). There can be many reasons for item non-response including accidentally missing a question, turning two pages at a time, and not knowing the answer or not wanting to respond because the question is considered to be too personal or sensitive (Brick and Kalton, 1996). When dealing with item non-response it is important to understand in what sense the data is missing (missing at random (MAR) or missing not at random (MNAR)) and this will be discussed section 4.7.2. In the cross-sectional study item non-response may be a problem; how much of an issue this creates during analysis depends on which items are missing. For instance, if the items relating to the outcome of interest are missing, it will create more issues than if data on ethnicity is missing.

Improving response rates

A Cochrane review identified 481 trials, evaluating 110 different strategies for improving response rates (75 strategies were evaluated on more than 1000 participants) (Edwards et al., 2009). The strategies that were found to increase response rate included: providing monetary incentives, personalising invitations to

participants, using a first class stamp rather than franking, including a second questionnaire with reminders, having University sponsorship, the topic being of interest to participants, pre-notification prior to receiving the questionnaire and also shorter questionnaires, see Table 4-4 (Edwards et al., 2009). The information from the systematic review was taken into account during the development of the questionnaire for the cross-sectional study. The covering letter used to introduce the study is also important in securing responses to a questionnaire and it is important to explain how the participant was identified, outline study aims, confidentiality and the importance of the participants response (Bowling, 2014c).

*Table 4-4 Methods for increasing response rate in postal questionnaires information from Edwards et al 2009. Significant results are indicated by a **

Method	Odds Ratio (95% CI) Final Response	P value	Heterogeneity (I^2 Statistic)
Monetary incentive*	1.87 (1.73, 2.04)	P<0.00001	I^2 = 84%
Recorded delivery*	1.76 (1.43, 2.18)	P<0.00001	I^2 = 71%
Teaser on the envelope *	3.08 (1.27, 7.44)	P = 0.013	Single Study
Interesting topic*	2.00 (1.32, 3.04)	P = 0.0012	I^2 = 80%
Pre-notification*	1.45 (1.29, 1.63)	P < 0.00001	I^2 = 89%
F/U contact*	1.35 (1.18, 1.55)	P = 0.000015	I^2 = 76%
Unconditional incentives*	1.61 (1.36, 1.89)	P < 0.00001	I^2=88%
Shorter questionnaires*	1.64 (1.43, 1.87)	P < 0.00001	I^2=91%
Second copy of questionnaire at f/u*	1.46 (1.13, 1.90)	P = 0.0040	I^2=82%
Mentioning an obligation to respond	1.61 (1.16, 2.22)	P = 0.95	I^2=0%
University sponsorship*	1.32 (1.13, 1.54)	P = 0.00043	I^2 = 83%
Non-monetary incentive*	1.15 (1.08, 1.22)	P < 0.00001	I^2 = 79%
Personalised questionnaires*	1.14 (1.07, 1.22)	P = 0.000075	I^2 = 63%
Hand-written addresses*	1.25 (1.08, 1.45)	P = 0.0023	I^2 =14%
Stamped returned envelope vs franked*	1.24 (1.14, 1.35)	P < 0.00001	I^2 = 69%
Stamped outward envelope vs franked	0.95 (0.88, 1.03)	P = 0.20	I^2 = 0.0%
Assurance of confidentiality*	1.35 (1.24, 1.42)	P < 0.00001	Single Study
Anonymous vs Non Anonymous	0.96 (0.66, 1.39)	P = 0.06	I^2 = 72%
First class outward mailing*	1.11 (1.02, 1.21)	P = 0.015	I^2 = 0%
Sensitive questions *	0.94 (0.88, 1.00)	P = 0.035	I^2 = 0%
Mention obligation to respond vs none	1.61 (1.16, 2.22)	P = 0.0042	I^2 = 0.0%
Veiled threat in letter vs none*	2.09 (1.49, 2.93)	P = 0.0000021	Single Study
Response deadline given vs no deadline	1.00 (0.84, 1.19)	P = 0.98	I^2 = 48%
Sent by GP vs by research group	1.52 (0.73, 3.15)	P = 0.26	I^2 = 84%
Hand written vs non handwritten signature*	1.23 (1.08, 1.41)	P = 0.0017	I^2 = 62%

Method	Odds Ratio (95% CI) Final Response	P value	Heterogeneity (I^2 Statistic)
Open vs closed questions	0.31 (0.09, 1.04)	P = 0.057	I^2 = 96%
Easy question first vs last*	1.61 (1.14, 2.26)	P = 0.0068	I^2 = 0.0%
Demographics first vs last	1.08 (0.94, 1.25)	P = 0.26	I^2 = 7%
More relevant questions first vs last*	1.23 (1.10, 1.37)	P = 0.00037	Single Study
High quality vs standard quality paper	0.8 (0.6, 1.06)	P = 0.12	I^2 =0.0%
Folder or booklet vs stapled	1.10 (0.99, 1.23)	P =0 .079	I^2 = 0.0%

4.7.2 Missing data

Missing data is an issue in most research with populations of people. It can be categorised into three types: missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). It is important when confronted with missing data to know which type of missingness applies as this affects the way it can be dealt with. This will be important in the cross-sectional study as by its very nature there is likely to be both unit and item non-response, contributing to missing data. Data that is MCAR has no relation to any variables in the analysis (including exposure, outcome or confounders), this causes loss of statistical power but estimates are not biased (Kristman et al., 2016). Data that is MAR is where the likelihood of that data being missing is not related to the missing factor, but it is related to the other variables. The missing data can be assumed to be split evenly between the groups of interest and will have a similar lack of effect on the results of the study as MCAR (Kristman et al., 2016). Data that is MNAR is directly related to the variable of interest, for instance those with depression who may be less likely to report mental health conditions than those without depression. The missing data is related directly to the outcome of interest and cannot be explained by other factors, so it is important that this is taken into account during analysis (Kristman et al., 2016). This is the most important type of missing data and even small amounts can cause significant bias (Kristman et al., 2016). When data is MNAR, groups can self-select (either to respond or not respond) and you can end up with narrow 95% CI around results which can lead to overconfidence that they represent the true results (Kristman et al., 2016).

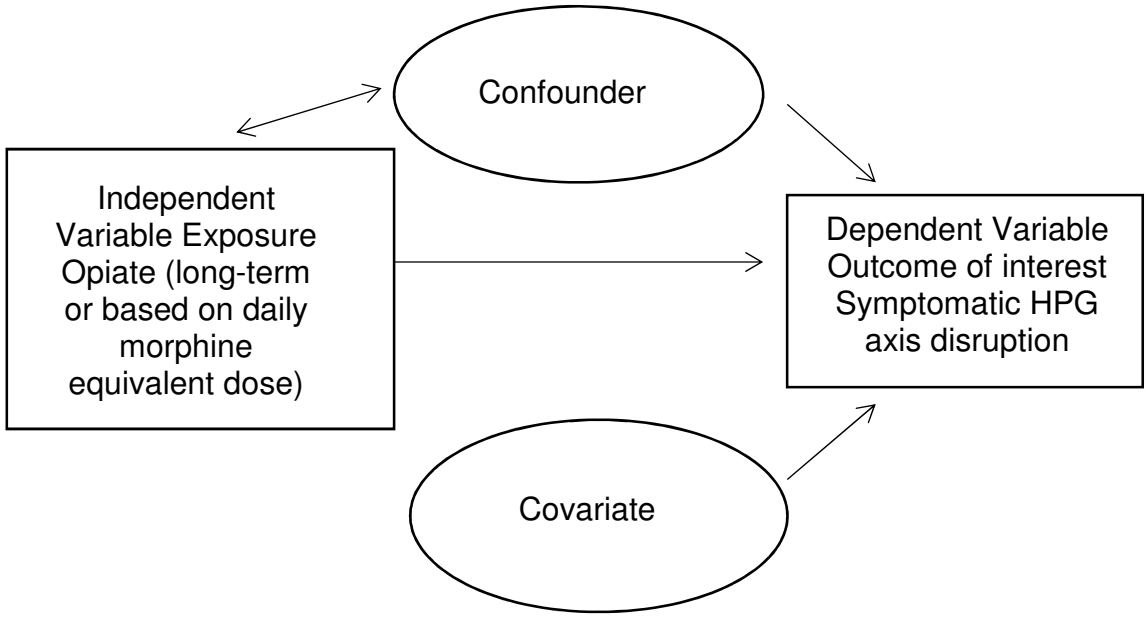
Dealing with missing data

The most important step when dealing with missing data is to decrease its occurrence in the first place and this should be considered at all stages of the study design process (Brick and Kalton, 1996). One method for dealing with missing data is through imputation, which essentially allows the missing values to be replaced. The crudest way to do this is with the average result for the sample but it can be done with prediction equations (Berg, 2005; Brick and Kalton, 1996). The major drawback to imputation is that the precision of results will be better than expected as most imputation methods are computed by averaging other observations and this means observations included are more similar than if all the results were true observations (Berg, 2005). When imputed data are used in traditional statistical methods, the sample size will use imputed values as well as true values which will create tighter standard errors and inflated significance tests (Berg, 2005). Weighting is another way to deal with missing data by discarding partial observations and assigning a weight to each complete observation in order to balance the sample; for instance if a certain characteristic is present in equal amounts in the population but the sample has a 2:1 split, the underrepresented characteristic would be weighted to make the sample more representative of the population of interest (Berg, 2005). A further approach is the maximum-likelihood approach which uses probability distribution. This makes an assumption of the distribution of the sample and then this is used to calculate missing data values. Maximum-likelihood makes a strong assumption about the probability distribution generating random survey responses (Berg, 2005).

4.7.3 Confounding

Confounding occurs when exposure and outcome are both related to a third factor that is not on the causal pathway under investigation but may affect any association seen (see Figure 4-7). The confounder will interact with the independent variable/exposure and the outcome (Bowling, 2014a; Delgado-Rodriguez and Llorca, 2004; Jager et al., 2008). Confounding can lead to the level of risk associated with an exposure of interest being either over or underestimated, and affects the validity of any investigation into cause and effect (Blumenthal et al., 2001; Signorello et al., 2002). During the design phase of any epidemiological study it is important to consider possible confounding factors. These can either be controlled for during matching or information can be collected on these specific factors and then they can be included in statistical analysis (e.g. through multiple logistic regression). Confounding factors can be anything, for instance the environment, medicine, diet, genetics and medical conditions, which means it can be difficult to account for all possible confounders. In a perfect world research could be undertaken by just altering a single factor at once and seeing what effect it has. However this is not possible in epidemiological research as most studies are purely observational (Blumenthal et al., 2001; Coggon et al., 2003). In the case of this thesis the independent exposure is the use of opioids (either split by duration or daily morphine equivalent dose), and the dependent outcome of interest is symptomatic HPG axis disruption (reproductive and sexual dysfunction). Covariates need to be considered, and these are factors that can cause the outcome of interest but do not lie on the direct causal pathway under investigation, they are unrelated to the exposure.

Figure 4-7 Confounders and their relationship with independent and dependent variables adapted from (Bowling, 2014a)



Confounding by indication is common in epidemiological studies of interventions (Signorello et al., 2002) and is introduced when the indication for the exposure is also a risk factor for the outcome of interest. This type of bias occurs mainly in retrospective observational studies, so it is an important issue for the cohort study undertaken as part of this thesis (Delgado-Rodriguez and Llorca, 2004). As a treatment is being prescribed (opioids) there will always be an indication for this treatment and the choice to offer treatment can be complex. Factors that can affect whether a treatment is provided are: disease severity, stage, symptoms, current treatment, previous failed treatments, individual preferences and clinician treatment preferences (Signorello et al., 2002). It is often the case that dependent on the severity of a disease, different treatments may be recommended. This is the case with musculoskeletal conditions where guidelines recommend simple analgesia

(paracetamol and topical NSAIDs) as a first line treatment, then oral NSAIDs, and then opioids only if simple analgesics have failed (National Institute for Health and Care Excellence, 2014a; Signorello et al., 2002). Confounding by indication can be difficult to deal with in observational studies but careful statistical analysis can go some way to balancing the effect (Signorello et al., 2002).

Methods to control confounding

Confounding should be taken into account during the design of studies (through randomization, matching and restriction) and during analysis (through multiple regression, stratification or standardization) (Jager et al., 2008). Within observational studies, it is possible to use matching and restriction during the design phase, whereas randomization of patients to treatment groups is only possible within interventional studies (Jager et al., 2008). It is important that confounding is considered during the design phase, as it is not always possible to fully account for confounding during analysis and this can lead to residual confounding (Smith and Phillips, 1992). Residual confounding is where the design or analysis is unable to fully account for confounding factors (because for instance a confounder was not considered, data were not complete or it was not possible to measure a particular confounder), and this still has an effect on the results of the study (Jager et al., 2008).

As mentioned above, matching for characteristics that may be confounders (e.g. age, sex) can decrease the potential for confounding. Another way is to restrict those selected to participate through inclusion or exclusion criteria (Jager et al., 2008). For instance, it may be predetermined that only patients aged 20-40 years are included, or any patients with pre-existing cancer excluded. This decreases differences

between study groups but may mean that the results are less generalisable (Jager et al., 2008). The cohort study will be matched for year and age at the start of opioid use (split by opioid duration), practice and having a coded musculoskeletal condition in order to make the two groups similar without over matching and restricting those that can be included within the cohort. It will ensure that all those included have no contraindications to opioid use.

During the analysis phase of a study, confounding can be dealt with using several different methods including multiple logistic regression (within the cross-sectional study logistic regression will be used as this allows analysis of a binary outcome), stratification and standardisation. Stratification divides a study population into subgroups based on a specific confounder, following which relative risks are calculated per subgroup. Stratification is useful when there are only a small number of confounders to adjust for. However with continuous variables, residual confounding is likely to remain, for instance if age is dichotomised at 50 years, there is likely to be difference remaining in the two subgroups (Jager et al., 2008). Standardisation takes account of confounding factors by creating weighted averages for different groups (e.g. age groups) and then calculating an overall adjusted effect size (Jager et al., 2008; Stewart, 2010). Standardisation can account for confounders including age and sex, in order to eliminate the effect of the confounding factor on the analysis (Coggon et al., 2003). Statistical analysis using regression models can also be used to adjust for confounders, as it holds all other factors constant whilst assessing the independent variable of interest (Bowling, 2014a; Smith and Phillips, 1992). Multivariable logistic regression will be used in the analysis of the postal survey (see section 4.4.2 for further details) and Cox regression models will be used

in analysis of the CPRD cohort study (see section 4.5.1); these will be used to understand associations and adjust for potential confounding factors.

4.8 Summary

Epidemiology can be used to study the distribution of disease in different populations, and the differences between population groups. There are many different techniques used in epidemiological research. In this thesis the two methods that will be used are a cohort study utilising primary care consultation data collected routinely and a cross-sectional postal survey collecting new data specifically for this research project. The issues when designing these types of research have been discussed above and will be taken into account during the design phase of each study.

5 Cohort study methods

5.1 Introduction

As previously discussed in chapter one, long-term opioid use in men is associated with hypogonadotrophic hypogonadism known as OPIAD (Abs et al., 2000; Aloisi et al., 2009; Benyamin et al., 2008; Daniell, 2002; Smith and Elliott, 2012). The systematic review in chapter three has shown limited evidence for this in women, but it has highlighted that there is a potential link requiring further investigation.

5.2 Aim

To assess if long-term opioid use for musculoskeletal pain is associated with reproductive and sexual dysfunction when compared with short-term opioid use, specifically symptomatic disruption of the hypothalamic-pituitary-gonadal axis in women, 18-55 years old.

5.3 Objectives

1. To investigate the prevalence of reproductive and sexual dysfunction among women 18 to 55 years old receiving opioids (long-term and short-term) for musculoskeletal pain, through a matched cohort from CPRD with linked HES data.
2. To determine if women aged 18 to 55 years old prescribed long-term opioids for musculoskeletal pain, when compared to women receiving short-term opioids, are more at risk of developing reproductive and sexual dysfunction. Reproductive and sexual dysfunction within this cohort study specifically refers to menstrual irregularities, menopause (and symptoms of menopause), low libido and infertility.

5.4 Clinical practice research datalink (CPRD)

CPRD is a large UK primary care database which contains high-quality, anonymised information on over 11 million patients from over 600 general practices. There are currently between 4 and 5 million active patients (alive and currently registered with a CPRD practice). The data available from CPRD includes demographics, investigations, diagnoses, symptoms, referrals and prescribed medicines (Herrett et al., 2015). Prior to 2012 CPRD was known as the General Practice Research Database (GPRD). CPRD can also be linked to access information from HES data (which uses ICD-10 clinical coding for recording secondary care contacts) and Office for National Statistics (ONS) for death registries. These linked databases will be used for outcomes and information on deaths (Database, 2015; Health and Social Care Information Centre, 2015a; Herrett et al., 2015). The structure of healthcare within the UK means that primary care databases provide almost complete coverage; over 98% of the population are registered with GP's who act as gatekeepers to secondary care and record the outcome of any such care (Garcia Rodriguez and Perez Gutthann, 1997; Herrett et al., 2015; Williams et al., 2012). CPRD has been compared with data from the UK census (age, ethnicity and sex) and found to be broadly representative of the UK population (Herrett et al., 2010). CPRD provides high quality data as practices are required to reach a set standard in recording quality prior to contributing data. There are specific rules for coding data in CPRD, for example, diagnoses need only be coded on first presentation, if there is a treatment change or if another significant event occurs (Jordan et al., 2006). There are ongoing quality checks following the inclusion of a practice in CPRD to ensure that the data continues to meet the required standard for individual patients and the practice (Herrett et al., 2010). This cohort included only practices with HES and ONS linkage

(n=350). Practices with linkage have been shown to be similar to practices without linkage when comparing follow-up, prescribed medicine and demographics (Gallagher et al., 2011).

5.4.1 Validity of CPRD

CPRD has been externally validated in previous studies. A systematic review in 2009 found that estimates for validity were high, but the reporting of the methods was often unclear; the median proportion of confirmed diagnoses was 89% over 357 validation studies (Herrett et al., 2010). Other studies have evaluated the completeness of data in musculoskeletal disorders which is pertinent to the identification of patients included in the cohort study undertaken for this thesis (Jordan et al., 2006). This study compared the forerunner of CPRD which was known as GPRD with three other databases, two national and one local to estimate prevalence of rheumatoid arthritis, osteoarthritis and arthralgia. GPRD estimated a lower prevalence of all conditions in comparison with the other databases. This was thought to be due to the difference in coding instructions, with GPRD allowing symptom codes if the diagnosis is uncertain, whereas the other databases encourage diagnostic coding. As discussed above, GPRD also only requires coding of diagnosis at first presentation and significant events, which means there is potential for missing data, as patients with stable chronic conditions may not have presented to the healthcare practitioner during the study period (Jordan et al., 2006). Additionally, patients with new conditions may not present to primary care, but may self-manage their condition in the community, although this issue affects all primary care databases (Last, 1963).

Prescriptions are generated electronically and recorded automatically by UK primary care systems, so the only medicines not included in the database will be those that

can be purchased from pharmacists without a prescription ("over the counter" medicines, of which the only "over the counter" opioids available are low dose co-codamol and dihydrocodeine for a maximum of 3 days/32 tablets for acute pain), and handwritten prescriptions or medicines prescribed from secondary care (although there is a facility to record these prescriptions within GP computer systems) (Garcia Rodriguez and Perez Gutthann, 1997; Herrett et al., 2010; Jordan et al., 2006; Medicines and Healthcare products Regulatory Agency, 2009).

5.4.2 Advantages

One advantage of using CPRD is that it is a large database. This was important for this study as the outcomes of interest have low rates in the general population (premature ovarian failure has a prevalence of 1%). Therefore, in order to have enough power for statistical analysis, a large number of subjects was required (Luborsky et al., 2003). As well as having a substantial population of subjects, CPRD has over 79 million person years of follow-up and individual patients have a median follow-up period of 9.4 years (IQR 3.4-13.9) (Herrett et al., 2010).

5.4.3 Limitations

Use of databases for research can mean that there is the potential for missing data and there are a few specific considerations related to the use of databases with this study. The nature of missing data in databases can be a complex issue because the data may be missing in different proportions in different groups. For instance, with blood pressure (BP) measurements, the quality outcomes framework (QoF, a voluntary annual rewards scheme with certain indicators for UK GPs) asks for yearly BP measurements in patients with hypertension and every five years in healthy

patients over 45 years old, but there is no requirements for BP in well patients under 45 years old. QoF requirements can change year on year (National Health Service, 2017; NHS, 2015).

CPRD does not have the facility to identify whether prescriptions are specifically for a particular condition, however it does require coding of a condition when changing treatment regimen so there should be a temporal relationship between a prescription and a coded condition (Jordan et al., 2006).

5.5 Hospital episode statistics database

HES contains information on hospital admissions, outpatient appointments and Accident and Emergency attendances in England. Every year HES processes 125 million patient records. The primary function of HES data is to ensure that the hospitals are paid for the work that they do, but the database is also available for research. HES was conceived in 1987 to provide national data on all episodes of hospital care delivered in England (Health and Social Care Information Centre, 2015a). Not all CPRD data is linked to HES; only 58% of CPRD practices have consented to data linkage, but, as mentioned above, this subset of practices is comparable to the whole of CPRD (Herrett et al., 2015).

5.6 Study population

This cohort study used a subset of participants from a previously defined population used in a similar cohort study examining the use of long-term opioid prescribing and adverse effects (Bedson et al., 2016, 2019a). Subjects were included in the original cohort if they:

1. Started long-term use of opioids between 2002 and 2013. Long-term opioid use was defined as the issue of three opioid prescriptions within 90 days from and including the first date of a new prescription for opioids (provided there was no opioid prescription in the preceding six months). A period of opioid use ended if there was a gap of more than six months from last use of opioids (28 days after the issue of the last prescription since prescribing guidelines from the NHS Business Services Authority for prescription of controlled drugs state that no more than a 28 day supply should be given except in exceptional circumstances) (NHS Business Services Authority, 2014). This is in line with definitions used in previous epidemiological studies (Dunn et al., 2010; Von Korff et al., 2008). A new episode of opioid use occurs if there was no opioid use in the preceding six months. Opioids were defined as analgesics for moderate and severe pain and were identified from sections 4.7.1 and 4.7.2 of the British National Formulary (BNF) (BNF, 2018a). This includes weak to very strong opioids and both short and long-acting opioids (these were defined in Section 1.3).
2. Participants must have had a recorded non-inflammatory musculoskeletal problem in primary care in the period 14 days before the index opioid prescription to 90 days following this. Musculoskeletal pain was chosen as the indication for opioids rather than all cause CNCP in order to provide a more homogenous group of study participants, and to partly address the issue of confounding by indication (see Section 4.7.3 for definition and further information). Musculoskeletal conditions have been identified as the underlying cause for CNCP in 40% of UK CNCP patients, and one in seven primary care consultations are for a musculoskeletal condition, so this represent a significant proportion of patients attending UK primary care (Breivik et al., 2006; Jordan et al., 2010). The time

period for the musculoskeletal condition being coded and the opioid being prescribed ensured that there was a temporal relationship between the musculoskeletal problem and index opioid prescription, particularly due to the need to code a condition when changing treatment regimen in CPRD (Jordan et al., 2006).

3. Aged 18 years or over at initial prescription.
4. At least 12 months of records in the CPRD database prior to the initial opioid prescription.
5. No record of cancer prior to prescription or within six months following the index opioid prescription. Patients were censored if they had a cancer diagnosis following inclusion in the cohort.
6. Registered at a CPRD general practice that consented to linkage to other datasets (as outcomes for the original cohort were partially identified from the integrated HES data and office of national statistics (ONS) data for patient deaths).

The cohort was prepared based on the above criteria for the larger study (Bedson et al., 2016, 2019a). A short-term opioid group was matched for year of birth (± five years), sex, practice and first year of opioid use (± two years). Short-term opioid users had not used long-term opioids but had been prescribed opioids that did not fit the criteria described above for the subject to be considered a long-term opioid user. The study carried out for this thesis included a subgroup of patients fulfilling the above criteria, who additionally were women and aged between 18 and 55 years old at first opioid prescription; the inclusion and exclusion criteria are summarised in Table 5-1. The cohort was developed for the larger study and the database was

received by the author (ER) for analysis, prepared, and limited to women 18 to 55 years old (undertaken by YC).

Table 5-1 Cohort inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Women Age 18-55 years old at initial opioid prescription Starting a period of long-term opioid use Coded musculoskeletal condition from 14 days before to 90 days after initial opioid prescription Linked HES and ONS data	Cancer diagnosis at any time prior to study or within the first six months of opioid prescription Less than 12 months of records within CPRD prior to first day of opioid prescription

5.7 Study outcomes

The outcomes of interest were defined following the systematic review reported in Chapter 3. The outcomes of interest were abnormal menstruation (amenorrhoea or oligomenorrhoea), decreased libido (female sexual dysfunction), menopause and infertility. Despite infertility not being a condition highlighted from the systematic review, it has been included as an outcome as it is a significant clinical feature of women with hypogonadotrophic hypogonadism (Messinis, 2005). Premature ovarian failure was not identified separately from menopause in the review as an outcome, but it is also a potential outcome if opioids interfere with the HPG axis and is also a reason that women may present to the GP. Following identifying the outcomes of interest, these conditions were then identified from CPRD using Read Codes. Read Codes are a “coded thesaurus of clinical terms and have been used in the NHS since

1985… they provide the standard vocabulary by which clinicians can record patient findings and procedures in health and social care IT (information technology) systems across primary and secondary care" (Health and Social Care Information Centre 2015b, Read Codes). Reasons for consultation, investigations and diagnoses, are coded using Read Codes in CPRD.

ER performed a search in the clinical terminology browser to develop an initial list of Read Codes. The clinical terminology browser was the 5 byte version 2 (2014-10-01) and it uses ReadEngine which is a copyrighted browser. Using the Read Code browser, Read Codes relevant to the outcomes of interest were identified (the full list can be found in Appendix 6). Relevant Read Codes were exported to Microsoft Excel, and reviewed for relevance by ER and refined with input from another primary care clinician (JB) (Microsoft, 2013b). Data on outcomes was collected from day 90 of opioid use up to five years of follow-up. The same conditions were identified from one year before opioid prescription and used in statistical analysis as pre-existing conditions. This information was searched for in CPRD and added to the study database by the study statistical advisor (YC).

5.8 Covariate data

The systematic review, a search for literature regarding the outcomes of interests, and professional knowledge had revealed a wide range of possible confounding factors and covariates that needed to be taken into account during the design of the study.

Data on comorbidities was collected from between 12 months before and three months after initial opioid prescription, comorbidity was identified using three different

methods. Comorbidity is defined on the basic premise that a patient has two or more simultaneous clinical conditions (Valderas et al., 2008). Firstly, the outcomes of interest were considered as comorbidities if they occurred prior to the start of follow-up, and they were identified in the same way as described above for identifying outcomes. Secondly, the following specific covariate conditions were also identified: thyroid conditions, low BMI (<18), adrenal conditions (e.g. adrenocortical insufficiency), obesity (as a coded condition), structural gynaecology conditions (e.g. PCOS), illegal opioid misuse and BMI (categorised as <25 kg/m2, ≥25 kg/m2 (overweight) or missing, where multiple values were recorded the value closest to the start of follow-up was used). Depression and anxiety were not included as specific covariates and treatments including antidepressants were not included separately from total number of prescriptions, as it was not considered during the development of the cohort. The limitations of this will be discussed in Chapter 7. Finally the total number of prescriptions was mapped to BNF sections and the number of sections prescribed from was used as a surrogate for the number of comorbid conditions (Perkins et al., 2004). NSAID use was also assessed since research looking at use of NSAIDs in chronic back pain has found that women using short-term NSAIDs for ten days had failed to ovulate (6.5% of those taking naproxen and 27.3% eterocoxib) compared to women receiving placebo who ovulated (Salman et al., 2015). Data was collected on NSAID use for four months prior to the start of follow-up, see Figure 5-1 for a GANT chart showing the timeline of data collection for the study.

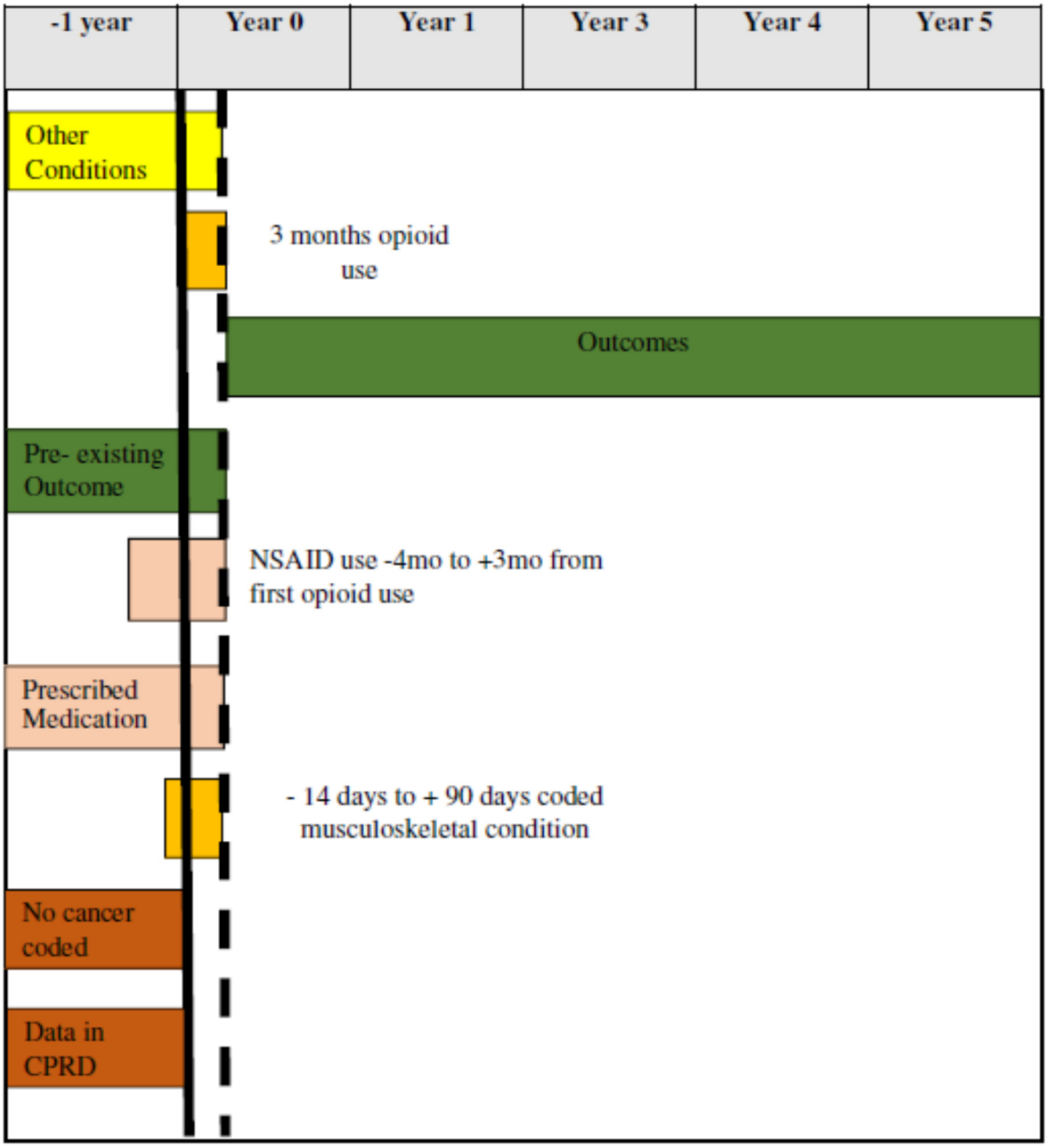
Data on smoking and alcohol use was identified in the year prior to first opioid prescription and up to the start of follow-up. They were both categorised as ever, never or missing.

5.9 Preparing the database

A matched cohort was already available for patients taking long-term opioids compared to those who had taken short-term opioids as defined previously. This cohort was limited to include women between 18 and 55 years of age.

The Read Codes for associated conditions and outcomes were initially identified through the clinical terminology browser by ER and when a code was found, the sub codes and parent codes were reviewed to see if they should be included by two reviewers (ER and JB). The Read Codes are not compatible with the CPRD database so needed to be converted to medcodes (which are numerical codes that are unique to CPRD and have equivalent alphanumerical Read Codes) that could be searched for within the database (Watson et al., 2017). The Read Codes were also converted to ICD-10 codes for searching data from HES. The search within CPRD was undertaken by YC based on Read Codes provided by ER (see Appendix 6).

Figure 5-1 Gant chart showing cohort study timeline. Solid line shows day of initial opioid prescription, Dotted line shows the start of follow-up.



5.10 Statistics

The sample size (198000) of the initial cohort (from which this study sample was taken) was calculated to have a power of 80% to detect a hazard ratio of 1.2 for the rarest adverse event being studied which was opioid overdose with an adverse rate

of 50/10,000 persons. The rate of the rarest outcomes in the sub study reported here is premature ovarian failure, which affects 1% of the population (Luborsky et al., 2003) and amenorrhoea affecting 3-4% of the population. The population included in this study was 44260 (22130 long-term and short-term users) (The Practice Committee of the American Society for Reproductive Medicine, 2008). A retrospective power calculation for each outcome using a 5% type 1 error rate and the actual data from each outcome shows that the power for the outcomes menstruation (power = 0.82) and menopause (power = 0.99) was sufficient, but for low libido (power = 0.10) and infertility (power = 0.09) was not. It is important to note that retrospective power calculations should not be used to help interpret results, as they are based on the assumption that the observed results are equal to the true values within the population (Hoenig and Heisey, 2001).

Statistical analysis of the data was performed using STATA 14.0 (StataCorp, 2017). When statistical tests were undertaken <0.05 (for two-tailed tests) was used as the level for statistical significance.

5.10.1 Demographics

The demographics of the women receiving long-term opioids and the women receiving short-term opioids were described using means and standard deviations if normally distributed and medians and interquartile ranges (IQR) if non–parametric. The demographics were compared using descriptive statistical tests, where two categorical variables were compared a chi-squared test was used, if the comparison included continuous variables a student's t test was used if the data was parametric, and a Wilcoxon-Mann-Whitney test for non-parametric data.

The cohort was split into age categories (18-25 years old, 26-35 years old, 36-45 years old and 46-55 years old) in order to describe the age distribution of the subjects within the study and for use in some of further analysis (as certain outcomes might be expected to occur more frequently in different age groups, for instance menopause would not be expected in 18-25 year olds). The age groups were not used as a covariate in Cox regression modelling, and age was included as a continuous variable. These categories were chosen based initially on the normal age for menopause, with those 45 years old and younger being considered early menopause (Chang et al., 2007). The age groups were evenly split (as far as possible) and 46 years and over included only women having a menopause at a "normal" age and then split at further 10-year gaps.

5.10.2 Covariates

Covariate conditions (defined above in section 5.8) were described using the number affected in long-term and short-term opioid groups and women across the entire cohort. Proportions in both groups and the entire database were calculated. Comparison of the proportions between long-term and short-term opioid users was undertaken using chi-squared statistics.

5.10.3 Outcomes

Basic descriptive statistics were performed for each outcome detailing the number of subjects affected in the whole cohort, the short-term and long-term opioid users. The proportions for those affected were calculated and presented with the 95% CI.

Analysis one calculated the incidence per 10,000-person years at risk. The incidence per 10,000-person years was calculated for the whole group, long-term

opioid users and short-term opioid users. Following this, the incidence per 10,000-person years was calculated for each age group.

Analysis two compared the level of risk dependent on duration of opioid use for the four outcomes of interest using survival analysis.

5.10.4 Survival analysis

Survival analysis was undertaken using the Cox proportional hazards model, described fully in section 4.5 (Cox, 1972). Cox proportional hazards models were chosen because they take into account time as a factor and estimate the risk over the whole time period rather than just the end point of the study. The proportional hazards assumption was tested through log-log plots and Schoenfeld residuals. Subjects within the analysis were censored if they had an outcome, left a CPRD registered practice, died, or the practice stopped contributing to CPRD. It was assumed that censored patients did not differ systematically from those that remained uncensored. Cox proportional hazards models assessed the differential risk of reproductive and sexual dysfunction between different groups of opioid users.

The initial Cox regression models were univariate looking at each of the four outcomes. This was done over the full five-year follow-up but also looked separately at year one, year two and years three to five, in order to assess if hazard differed with time. The Cox regression adjusted for associated factors including NSAID use, ethnicity, age, BMI (dichotomised at 25 representing those overweight and those of normal weight), smoking and the associated conditions identified above dependent on the numbers that were found in the earlier descriptive analysis of each associated condition (thyroid disease, pituitary conditions, hypothalamic conditions, adrenal

conditions, low BMI, structural gynaecological conditions and illegal opioid use). A Cox regression was undertaken for each covariate individually for each outcome and where the proportional hazards assumption was violated, those covariates were included as time-varying covariates (Bellera et al., 2010). All of the above were run over the full five-year follow-up and year one, year two and years three to five. Based on the age groups calculated earlier, if there were large differences in numbers with outcomes in each age group, the Cox regression was also run split by age but as this decreased the numbers for analysis it was dependent on the number with each outcome, as to whether it was appropriate to undertake this analysis.

Sensitivity analyses were undertaken using first a complete-case approach (where cases with missing data are removed from analysis), secondly removing those with pre-existing outcome conditions, and finally removing women with a coded diagnosis of menopause as a proxy for HRT use. An online convenience sampled survey on the website menopause matters found that 60% of respondents had used or were currently using HRT, so using a diagnosis of menopause as a proxy for HRT use does mean that more women were removed than necessary but it should have excluded all women who are currently receiving HRT (Cumming et al., 2015).

5.11 Summary

In this chapter the methods for the cohort study have been outlined. This chapter also discusses the important advantages and disadvantages that need to be considered when undertaking a database cohort study. In the following chapter the results of the cohort study will be discussed.

6 Cohort study results

This chapter presents the results of the CPRD cohort study undertaken for this thesis, the methods of which were presented in chapter 5. The cohort study investigated women aged 18-55 years old with a painful musculoskeletal condition and a prescribed opioid for possible sexual and reproductive dysfunction. There were four outcomes of interest within this study: abnormal menstruation, menopause, low libido and infertility. First the cohort is described and then the incidence rate and Cox regression for each outcome is presented.

6.1 Demographics

The cohort contained 44260 women in total. There were 22130 short-term opioid users and 22130 long-term opioid users. Table 6-1 shows comparisons between the two groups. No statistically significant difference was found between long-term and short-term opioid users for age or region which were matched for in the study design, but there were statistically significant differences when comparing ethnicity, NSAID use, BMI, smoking status, alcohol use and number of comorbidities.

6.1.1 Comorbidity and NSAID use

The median number of comorbidities in long-term opioid users was 8 (IQR 6, 12) compared with a median of 6 (IQR 4, 9) in short-term opioid users; the difference between the two groups was statistically significant ($p<0.01$). NSAIDs were prescribed to 57.5% (95% CI 56.8, 58.1) of long-term opioid users compared with short-term opioid users where 39.2% (95% CI 38.6, 39.9) were prescribed NSAIDs, this was a statistically significant difference ($p<0.01$) (Table 6-1).

Table 6-1 Study participant demographics split by duration of opioid use.

	Short-term opioids	Long-term opioids	P value
Number	22130	22130	
Ethnicity			
1 (White)	13,445, 60.8%	15,576, 70.4 %	<0.01
2 (Other)	1,226, 5.5%	1,158, 5.2%	
3 (Unknown)	7,459, 33.7%	5,396, 24.4%	
Region			
1 (North)	2,020, 9.1%	2,020, 9.1%	Matched
2 (Midlands and East England)	7,509, 33.9%	7,509, 33.9%	
3 (London)	5,905, 26.7%	5,905, 26.7%	
4 (South)	6,695, 30.3%	6,695, 30.3%	
Age*	43 (36, 49)	43 (35, 49)	Matched
NSAID			
0 (no prescription)	13446, 60.8%	9,407, 42.5%	<0.01
1 (NSAIDs prescribed)	8,684, 39.2%	12,723, 57.5%	
BMI*	26.3 (23.1, 30.7)	27.8 (23.9, 32.9)	<0.01˜
Comorbidities*	6 (4, 9)	8 (6, 12)	<0.01
Smoking status			
Never Smoked	11,504, 52.0%	9,944, 44.9%	<0.01
Ever Smoked	9,824, 44.4%	11,414, 51.6%	
Missing data	802, 3.6%	772, 3.5%	
Alcohol status			
Never Alcohol	2,721, 12.3%	3,070, 13.9%	<0.01
Ever Alcohol	17,531, 79.2%	17,154, 77.5%	
Missing data	1,878, 8.5%	1,906, 8.6%	

Figures are number in each group, percentage (95% CI) except in categories marked with a star where figures are Median (IQR). ˜ p value indicated is calculated using Wilcoxon-Mann-Whitney for non-normally distributed data. Other p values are Chi-squared.

6.1.2 Age

The age range for those included within the study was 18-55 years old. The median age was 43 years (IQR 36, 49) in long-term opioid users and 43 years (IQR 35, 49) in short-term opioid users. This study uses a maximum age of 55 years, the age was not normally distributed and reached a peak in the 46-55 year-old age group (see Figure 6-1). The subjects had been split into age groups to be used in later analysis and the number in each group is shown in Table 6-2.

Figure 6-1 Histogram showing age of study participants split by duration of opioid use

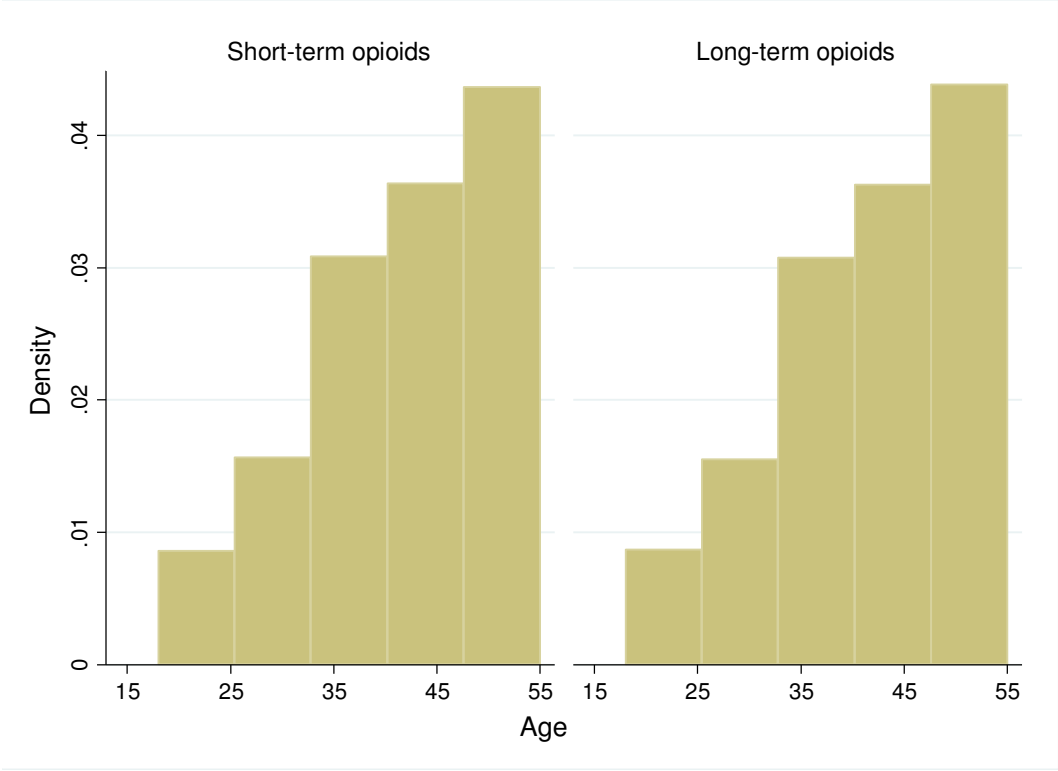


Table 6-2 Age groups split by duration of opioid use. Figures are number in each group, percentage

Age	Number of subjects		
	Short-term opioids	Long-term opioids	Total
18-55	22130	22130	44260
18-25	1,410, 6.4%	1,426, 6.4%	2,838, 6.4%
26-35	4,121, 18.6%	4,109, 18.6%	8,232, 18.6%
36-45	7,623, 34.4%	7,631, 34.5%	15,254, 34.5%
46-55	8,976, 40.6%	8,964, 40.6%	17,940, 40.5%

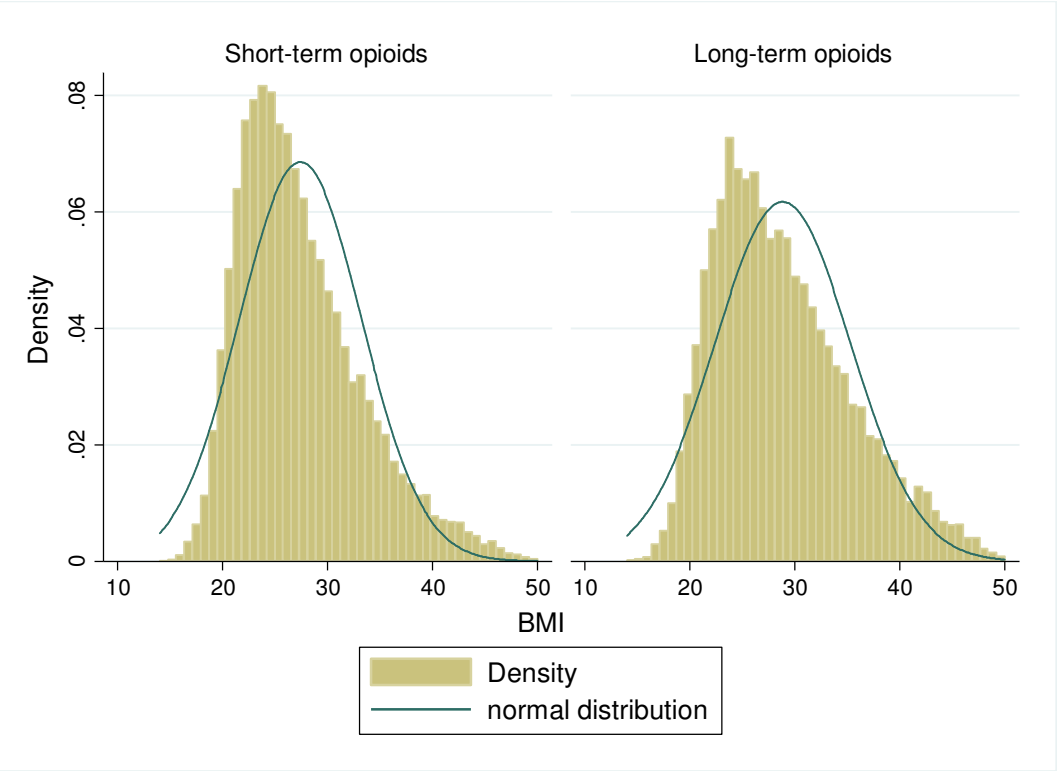
6.1.3 BMI

The median BMI in women receiving long-term opioids was 27.8 (IQR 23.9, 32.9), whereas in women who received short-term opioids the median was 26.3 (IQR 23.1, 30.7), the BMI was similar in both groups but the difference was statistically significant. BMI was not normally distributed within the cohort and data is skewed to the left (see Figure 6-2). BMI data was split into two groups for use in further analysis, using BMI's of < 25, and those ≥ 25 which represents the cut off between those women who are overweight and those considered of normal weight or underweight (see Table 6-3 for distribution). Table 6-3 also shows a cut off at BMI ≥ 30, this will not be used in further analysis but shows the number of obese women (defined by BMI ≥ 30) in each group. The number of women in each weight group is statistically significantly different between the long-term and short-term opioid users.

Table 6-3 BMI groups split by duration of opioid use. Figures are number in each group, percentage (95% CI)

	Short-term opioids	Long-term opioids	Total
BMI < 25	8,409, 38.0%	6,815, 30.8%	15,224, 34.4%
BMI ≥ 25 and <30	12,555, 56.7%	14,235, 64.3%	26,790, 60.5%
BMI ≥ 30	5,952, 28.4%	7,957, 37.8%	13,909, 33.1%
Missing data	1,166, 5.3%	1,080, 4.9%	2,246, 5.1%

Figure 6-2 Histogram showing BMI for participants split by duration of opioid use with line of normal distribution overlay.



6.2 Outcomes

6.2.1 Outcome counts and follow-up time

The outcomes of interest were: altered menstruation (less frequent or absent menstruation), decrease in libido, infertility and menopause/menopausal symptoms. The commonest outcome was menopause, affecting 10.6% of women across the whole cohort. Infertility affected the least number of subjects, identified in only 0.6% of women. The full distribution of the outcomes can be seen in Table 6-4. 27909 (63.1%) of women did not complete full five year follow-up due to reasons other than a recorded outcome and were censored; 27,521 women (62.2%) left a CPRD

practice before the full five year follow-up was completed and 388 (0.88%) women within the cohort died (see Table 6-5 for follow-up time).

Table 6-4 Distribution of outcomes of interest split by duration of opioid use. Figures are number with problem, percentage with problem (95% CI)

	Short-term opioids	Long-term opioids	Total
Altered Menstruation	1290, 5.8 (5.5, 6.1)	1432, 6.5 (6.2, 6.8)	2722, 6.2 (5.9, 6.4)
Libido	161, 0.7 (0.6, 0.8)	195, 0.9 (0.7, 1.0)	356, 0.8 (0.7, 0.9)
Infertility	135, 0.6 (0.5, 0.7)	116, 0.5 (0.4, 0.6)	251, 0.6 (0.6, 0.6)
Menopause	2245, 10.1 (9.8, 10.5)	2566, 11.6 (11.2, 12.0)	4811, 10.9 (10.6, 11.2)

Table 6-5 Follow-up time for each outcome of interest

Outcome	Median Follow-up time (days)	Interquartile Range
Menstruation	1193	552, 1825
Libido	1263	595, 1825
Infertility	1268	597, 1825
Menopause	1144	536, 1825

6.2.2 Rate of outcomes/10,000 person-years

Menstrual Cycle

Outcome number one was altered menstruation to less frequent or absent menstruation. This affected 2722 (44260) subjects, with a rate of 186.2/10,000 person-years (95% CI 176.4, 196.7) in short-term opioid users, and 209.5/10,000 person-years (95% CI 199.0, 220.7) in long-term opioid users (see Table 6-6). The rate of altered menstruation was found to be highest in younger age groups with a rate of 550.1/10,000 person-years (95% C.I. 479.7, 630.8) in 18-25 year olds receiving long-term opioids. The older the age group, the lower the rate, and in the 46-55 year old age group the rate fell below the rate for the group overall to 91.1/10,000 person-years (95% CI 83.7, 99.3), long-term users had higher rates across all age groups than short-term opioid users see Table 6-6.

Table 6-6 Rate of menstrual disturbance/10,000 person-years at risk

Age	Exposure Status	Menstrual Disturbance	Rate/10,000 person-years (95% CI)	Follow-up time person-years
18-55 years	Short-term opioids	1290	186.2 (176.4, 196.7)	69,264
	Long-term opioids	1432	209.5 (199.0, 220.7)	68,342
	Total	2722	197.8 (190.5, 205.4)	137,606
18-25 years	Short-term opioids	150	380.3 (324.0, 446.2)	3945
	Long-term opioids	205	550.1 (479.7, 630.8)	3727
	Total	355	462.8 (417.0, 513.5)	7671
26-35 years	Short-term opioids	326	267.1 (239.6, 297.7)	12,205
	Long-term opioids	368	302.6 (273.2, 335.2)	12,161
	Total	694	284.8 (264.4, 306.8)	24,365
36-45 years	Short-term opioids	540	224.2 (206.0, 243.9)	24,090
	Long-term opioids	607	255.4 (235.8, 276.5)	23,769
	Total	1147	239.7 (226.2, 253.9)	47,859
46-55 years	Short-term opioids	274	94.4 (83.9, 106.2)	29,025
	Long-term opioids	252	87.8 (77.6, 99.4)	28,686
	Total	526	91.1 (83.7, 99.3)	57,710

Libido

Outcome number two examined low libido. The rate of low libido in the whole cohort was 25.1/10,000 person-years (95% CI 22.7, 27.9), and the rate in long-term opioid users was 27.7/10,000 person-years (95% CI 24.0, 31.8), which is higher than the rate in those receiving short-term opioids of 22.6/10,000 person-years (95% CI 19.4, 26.4). In 36-45 year olds the difference in levels of low libido is more marked with long-term users at a rate of 34.1/10,000 person-years (95% CI 27.6, 42.3) and short-term users 20.2/10,000 person-years (95% CI 15.3, 26.6) and the CI does not cross, which indicates a statistically significant difference in this age group. It is important to note that even though the results were non-significant there is a consistent relationship with long-term opioid users having a higher rate of low libido than short-term users across all age groups apart from the oldest women (46-55 year olds). See Table 6-7 for a full summary.

Table 6-7 Rate of low libido/10,000 person-years at risk

Age	Exposure Status	Low libido	Rate/10,000 person-years (95% CI)	Follow-up time person-years
18-55	Short-term opioids	161	22.6 (19.4, 26.4)	71,095
	Long-term opioids	195	27.7 (24.0, 31.8)	70,470
	Total	356	25.1 (22.7, 27.9)	141,566
18-25	Short-term opioids	8	19.3 (9.7, 38.7)	4138
	Long-term opioids	9	22.1 (11.5, 42.5)	4065
	Total	17	20.7 (12.9, 33.3)	8203
26-35	Short-term opioids	31	24.4 (17.2, 34.7)	12,699
	Long-term opioids	36	28.2 (20.4, 39.1)	12,754
	Total	67	26.3 (20.7, 33.4)	25,453
36-45	Short-term opioids	50	20.2 (15.3, 26.6)	24,809
	Long-term opioids	84	34.1 (27.6, 42.3)	24,613
	Total	138	27.1 (22.9, 32.1)	49,722
46-55	Short-term opioids	72	24.4 (19.4, 30.8)	29,450
	Long-term opioids	66	22.7 (17.9, 28.9)	29,038
	Total	138	23.6 (20.0, 27.9)	58,655

Infertility

Outcome number three is concerned with infertility. The overall rate of infertility was 17.7/10,000 person-years (95% CI 15.6, 20.0). The rates were highest in 18-35 year olds with the rates decreasing in those over 36 years old. The results are summarised in Table 6-8. There was no clear difference in rates between long-term and short-term opioid users with the 95% CI overlapping (except in over 45 year olds where there were only three outcomes in total) and the rate/10,000 person-years being higher sometimes in short-term users and sometimes in long-term users.

Table 6-8 Rate of infertility/10,000 person-years at risk

Age	Exposure Status	Infertility	Rate/10,000 person-years (95% CI)	Follow-up time person-years
18-55	Short-term opioids	135	19.0 (16.0, 22.5)	71,177
	Long-term opioids	116	16.4 (13.7, 19.7)	70,642
	Total	249	17.7 (15.6, 20.0)	141,819
18-25	Short-term opioids	15	36.4 (22.0, 60.5)	4,116
	Long-term opioids	21	51.7 (33.7, 79.3)	4,059
	Total	36	44.0 (31.8, 61.1)	8,175
26-35	Short-term opioids	69	54.5 (43.1, 69.0)	12,653
	Long-term opioids	61	47.9 (37.3, 61.6)	12,726
	Total	130	51.2 (43.1, 60.8)	25,379
36-45	Short-term opioids	51	20.5 (15.6, 27.0)	24,819
	Long-term opioids	31	12.5 (8.8, 17.8)	24,712
	Total	82	16.6 (13.3, 20.6)	49,531
46-55	Short-term opioids	0	0.00	29,589
	Long-term opioids	3	1.0 (0.3, 3.2)	29,145
	Total	3	0.5 (0.2, 1.6)	58,734

Menopause

Outcome four looked at menopause and menopausal symptoms. Over the whole group, a rate of menopause of 357.1/10,000 person-years (95% CI 347.2, 367.4) was found; long-term opioid users had a higher rate of 383.7/10,000 person-years (95% CI 369.1, 398.8) compared to short-term opioid users whose rate was 330.9/10,000 person-years (95% CI 317.5, 344.8). Table 6-9 summarises the results over the different age groups. The number of woman affected under 36 years old is small with only three women affected in the 18-25 age group and 71 women in the 26-35 age group. The highest rates were seen in 45-55 year olds with a rate of 674.2/10,000 person-years (95% CI 643.5, 706.4) in long-term opioid users and 618.9/10,000 person-years (95% CI 589.9, 649.5) in short-term opioid users. A similar change is seen in the 35-45 year old age group but the rates are lower than in the 45-55 year olds. It is important again to note that the relationship is consistent across all age groups and there is a higher rate of menopause in long-term users when compared to short-term users.

Table 6-9 Rate of menopause/10,000 person-years at risk

Age	Exposure Status	Menopause	Rate/10,000 person-years (95% CI)	Follow-up time person-years
18-55	Short-term opioids	2245	330.9 (317.5, 344.8)	67,840
	Long-term opioids	2566	383.7 (369.1, 398.8)	66,875
	Total	4811	357.1 (347.2, 367.4)	134,715
18-25	Short-term opioids	0	0	4,144
	Long-term opioids	3	7.4 (2.4, 22.8)	4,081
	Total	3	3.6 (1.2, 11.3)	8,225
26-35	Short-term opioids	23	18.0 (12.0, 27.2)	12,744
	Long-term opioids	48	37.6 (28.3, 49.9)	12,760
	Total	71	27.8 (22.1, 35.1)	25,504
36-45	Short-term opioids	563	233.2 (214.7, 253.2)	24,147
	Long-term opioids	745	313.3 (291.6, 336.6)	23,782
	Total	1308	272.9 (258.5, 288.1)	47,930
46-55	Short-term opioids	1659	618.9 (589.9, 649.5)	26,804
	Long-term opioids	1770	674.2 (643.5, 706.4)	26,252
	Total	3429	646.3 (625.0, 668.3)	53,056

6.3 Covariates

This section describes the conditions that were adjusted for if appropriate during Cox regression. The number of subjects with each condition is shown in Table 6-10 and in all cases the proportion in the long-term opioids group was higher or the same as that in the short-term opioids group. Of the eight conditions, three had no statistically significant difference (general thyroid conditions, low BMI conditions and adrenal conditions) and the remaining five had a statistically significant difference in the proportion affected between long-term opioid users and short-term opioid users (hypothyroid, hyperthyroid, obesity, structural gynaecology conditions and opioid misuse), with long-term users affected more often.

Table 6-10 Associated conditions split by duration of opioid use. Figures are number with problem, percentage with problem (95% CI)

	Short-term opioids	Long-term opioids	Total	p
Non-specific thyroid conditions	52, 0.2 (0.2, 0.3)	58, 0.3 (0.2, 0.3)	110, 0.2 (0.2, 0.3)	0.57
Hypothyroid	353, 1.6 (1.4, 1.8)	551, 2.5 (2.3, 2.7)	904, 2.0 (1.9, 2.2)	<0.001
Hyperthyroid	45, 0.2 (0.2, 0.3)	76, 0.3 (0.3, 0.4)	121, 0.3 (0.2, 0.3)	0.01
Pituitary conditions	0, 0 (0, 0)	0, 0 (0, 0)	0, 0 (0, 0)	
Adrenal conditions	0, 0 (0, 0)	1, 0 (0, 0)	1,0 (0, 0)	0.32
Hypothalamic conditions	0, 0 (0, 0)	0, 0 (0, 0)	0, 0 (0, 0)	
Obesity	417, 1.9 (1.7, 2.1)	768, 3.5 (3.2, 3.7)	1185, 2.7 (2.5, 2.8)	0.00
Low BMI condition	27, 0.1 (0.1, 0.2)	36, 0.2 (0.1, 0.2)	63, 0.1 (0.1, 0.2)	0.26
Structural Gynaecology conditions	100, 0.5 (0.4, 0.5)	180, 0.8 (0.7, 0.9)	280, 0.6 (0.6, 0.7)	0.00
Illegal opioid use	6, 0.0 (0.0, 0.1)	44, 0.2 (0.2, 0.3)	50, 0.1 (0.1, 0.2)	0.00

P value calculated using Chi-squared comparison

6.4 Cox regression

The primary analysis of the outcomes was the Cox regression comparing long-term opioid users and short-term opioid users. The Cox regression was adjusted for the confounding factors identified (including associated conditions described in section 6.3 and demographic factors described in section 6.1).

Prior to undertaking Cox regression, the number of subjects with a coded confounding condition per group was calculated to guide whether they should be included in the Cox regression (see Table 6-10). No subjects had a recorded diagnosis of pituitary or hypothalamic conditions, and only one subject had a recorded adrenal condition so these were not included in the Cox regression model.

6.4.1 Menstruation

The proportional hazards assumption was tested using a Schoenfeld residual test which returned a non-significant p (0.38) value so the assumption was upheld for the unadjusted Cox regression comparing long-term and short-term opioid users for the outcome abnormal menstruation. A log-log plot and Kaplan-Meier graph were also produced (Figure 6-3 and Figure 6-4). The log-log plot was not parallel as you would expect if the proportional hazards assumption holds, it starts with a wide gap and the plots become closer and then cross. Consequently it was decided to run the Cox regressions over shorter periods of time as well as over the whole follow-up period (with time-varying covariates). Schoenfeld residuals were also calculated for each covariate included in the adjusted Cox regression model, and where the proportional hazards assumption was violated these covariates were included in the model for the full follow-up period as time varying covariates. The time varying covariates were

age, NSAID use, pre-existing menstrual disorders, hypothyroidism and structural gynaecological conditions (see Table 6-11). The issue of time varying covariates was also addressed by undertaking Cox regression using three different time periods: year one, year two and years three to five, this was an alternative to time varying covariates that were used over the full follow-up period. The median follow-up was 1193 days (Interquartile range (IQR) 552, 1825).

Figure 6-3 Log log plot for menstruation comparing duration of opioid use

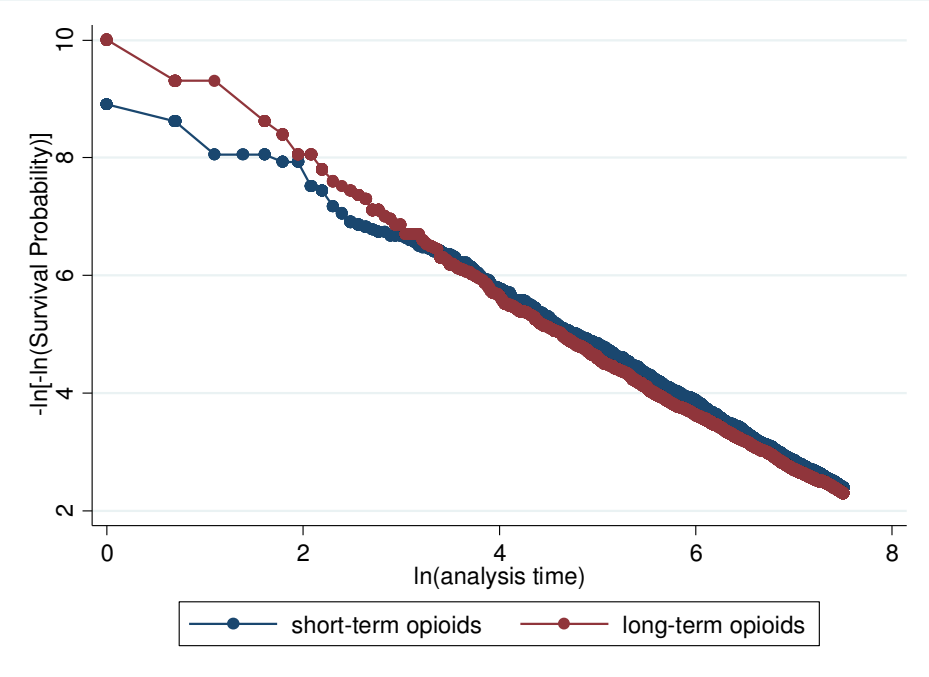


Figure 6-4 Kaplan-Meier curve for menstruation outcome comparing duration of opioid use

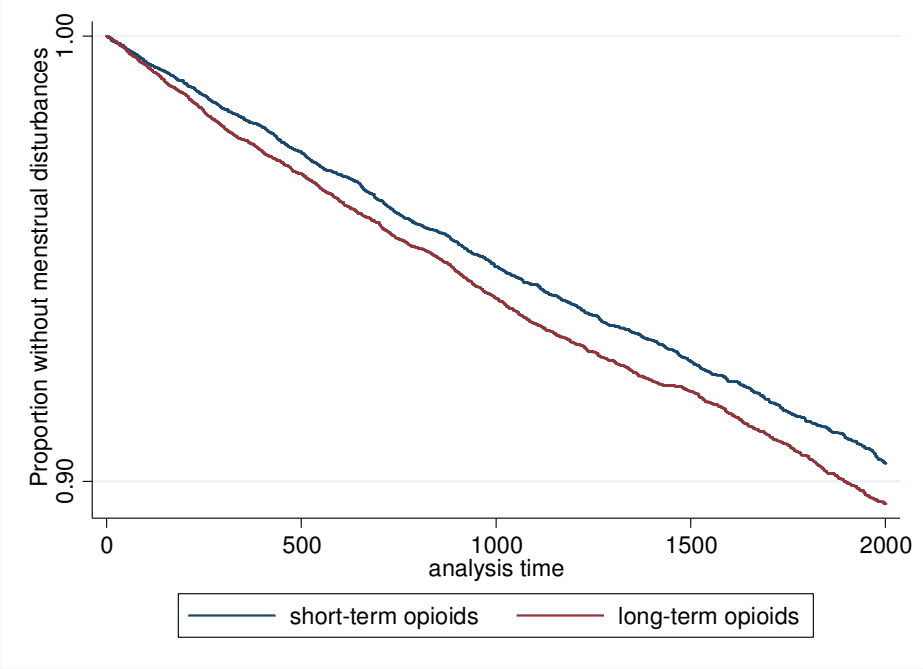


Table 6-11 Schoenfeld residuals for menstruation to test proportional hazards assumption prior to Cox regression for duration of opioid use

Variable	HR (95% CI)	Rho[$]	P value
Duration of opioid use	1.13 (1.05, 1.22)	0.02	0.43
Pre-existing menstrual disorders	2.34 (2.00, 2.73)	0.08	<0.001*
Thyroid conditions (not specified)	0.80 (0.33, 1.92)	0.01	0.62
Hypothyroid	0.97 (0.73, 1.29)	0.04	0.04*
Hyperthyroid	1.17 (0.58, 2.35)	0.01	0.74
Alcohol use ever	Reference		
Alcohol use never	0.86 (0.77, 0.96)	-0.03	0.20
Alcohol use not known	0.85 (0.72, 1.00)	-0.01	0.68
Smoker ever	Reference		
Smoker never	0.92 (0.85, 0.99)	-0.02	0.20
Smoking not known	0.97 (0.78, 1.23)	0.02	0.12
BMI <25	Reference		
BMI>= 25	1.05 (0.97, 1.14)	0.00	0.87
BMI missing	0.69 (0.56, 0.86)	0.02	0.40
Low BMI conditions	1.42 (0.71, 2.87)	0.04	0.03
Structural gynaecology conditions	1.31 (0.90, 1.89)	-0.05	0.01*
Illegal opioid use	2.22 (1.00, 4.96)	-0.01	0.48
No NSAID use	Reference		
Non-specific NSAID use	1.00 (0.92, 1.08)	0.01	0.73
COX2 NSAIDs	0.80 (0.66, 0.98)	-0.04	0.05*
Age	0.95 (0.94, 0.95)	-0.06	0.01*
Global test			<0.001

* indicates which variables were included as time-varying covariates based on the Schoenfeld residuals test $ indicates the Pearson product-moment correlation between the scaled Schoenfeld residuals and log(time) for each covariate.

The unadjusted Cox regression shown in Table 6-12 found a hazard ratio over the full five-year follow-up period of 1.13 (95% CI 1.05, 1.22), and 1.25 (95% CI 1.09, 1.42) in the first year; both were statistically significant. In the remaining time periods the hazard ratio was consistently more than 1 but the results were not statistically significant. Cox regression was adjusted for thyroid conditions, illegal opioid use, BMI, smoking status, alcohol use, NSAID use and the following time varying covariates (pre-existing menstrual disorders, hypothyroid conditions, low BMI, structural gynaecological conditions and age) over the full five year follow-up (Table 6-12). The result remained statistically significant over the full follow-up (1.13 (95% CI 1.05, 1.21) p < 0.001) and year one (1.23 (95% CI 1.07, 1.41) p <0.001).

Table 6-12 Cox regression comparing duration of opioid use for the outcome altered menstrual cycle

Follow-up	Hazard ratio (95% CI) unadjusted	P	Hazard ratio (95% CI) adjusted	P
5 years	1.13 (1.05, 1.22)	< 0.001	1.13 (1.05, 1.21)	<0.001
< 1 year	1.25 (1.09, 1.42)	< 0.001	1.23 (1.07, 1.41)	<0.001
1-2 years	1.06 (0.92, 1.24)	0.42	1.06 (0.91, 1.24)	0.45
3-5 years	1.08 (0.96, 1.21)	0.18	1.10 (0.99, 1.26)	0.08

The Cox regression for different age groups showed statistically significant hazard ratios in 18-45 year-olds see Table 6-13. Those women 46 years old and over had a hazard ratio that crossed 1 and did not show any increased risk of menstrual disturbances in women in the long-term opioid group compared with short-term opioid users. The largest hazard ratio was seen in 18-25 year olds, 1.37 (95% CI 1.13, 1.67) p <0.001. When adjusted for the covariate factors (thyroid conditions, illegal opioid use, BMI, smoking status, alcohol use, NSAID use and time varying covariates for pre-existing menstrual disturbance, hypothyroid, structural

gynaecological conditions, age and low BMI conditions) this was significant in all women less than 46 years old (Table 6-13).

Table 6-13 Cox Regression for menstrual disturbance and duration of opioid use split by age group for 5 year follow-up

Age Range (years)	Hazard ratio (95% CI) unadjusted	P	Hazard ratio (95% CI) adjusted	P
18-25	1.37 (1.13, 1.67)	<0.001	1.31 (1.07, 1.60)	0.01
26-35	1.15 (1.01, 1.32)	0.03	1.17 (1.02, 1.34)	0.02
36-45	1.13 (1.02, 1.25)	0.02	1.13 (1.02, 1.26)	0.02
46-55	0.93 (0.79, 1.10)	0.39	1.00 (0.85, 1.19)	0.96

Disturbance of menstruation had a higher hazard of occurring in women taking long-term opioids with this effect being statistically significant over the entire five year follow-up and the first year individually but not in year two or years three to five separately. The hazard ratio also remained above 1 after adjustment in women less than 46 years old. The relationship was statistically significant and showed the hazard of abnormal menstruation for women taking long-term opioids is higher than for women who received short-term opioids.

6.4.2 Libido

The proportional hazard assumption for unadjusted Cox regression was upheld with a non significant Schoenfeld residual (p=0.58). The asumption was also supported by the log log plot (Figure 6-5) which did not show the two plots crossing and the kaplan-meier graph (Figure 6-6) where again the plots did not cross. The plots diverge as time passes which supported the use of shorter time periods rather than just the five year follow-up. The Shoenfeld residuals checked prior to fitting the model for adjusted Cox regression showed that age should be included as a time varying covariate (see Table 6-14). The median follow-up time was 1263 days (IQR 595, 1825 days).

Figure 6-5 Log log plot for libido comparing duration of opioid use

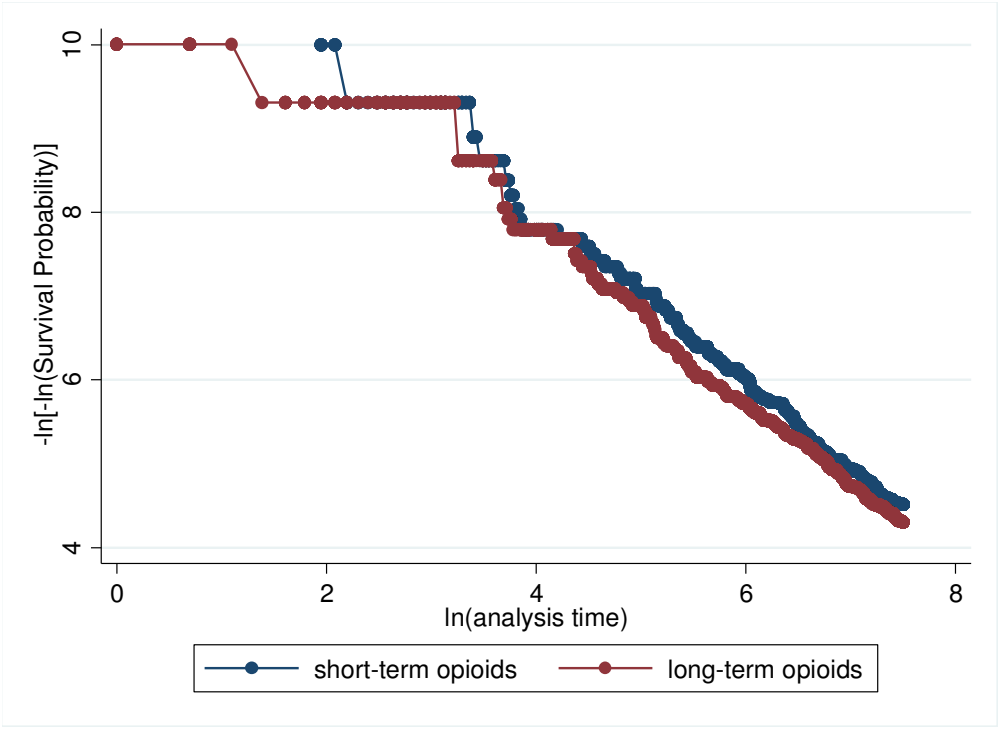


Figure 6-6 Kaplan-Meier curve for libido outcome comparing duration of opioid use

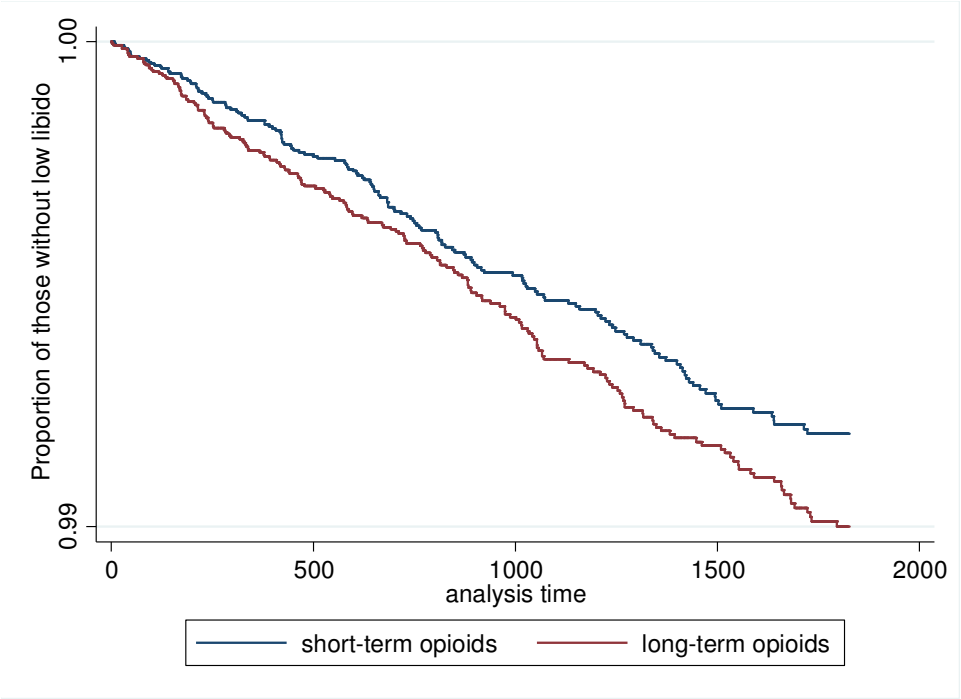


Table 6-14 Schoenfeld residuals testing the proportional hazards assumption for adjusted Cox regression for libido comparing duration of opioid use

Variable	HR (95% CI)	Rho	P value
Duration of opioid use	1.19 (0.96, 1.49)	0.005	0.93
Pre-existing libido disorders	14.11 (7.9, 25.1)	-0.09	0.10
Thyroid conditions (not specified hypo/hyper)	2.63 (0.65, 10.6)	-0.38	0.47
Hypothyroid	0.50 (0.18, 1.33)	0.068	0.20
Hyperthyroid	2.27 (0.56, 9.20)	-0.01	0.79
Alcohol use ever	Reference		
Alcohol use never	1.47 (1.03, 2.11)	-0.01	0.91
Alcohol use not known	1.11 (0.63, 1.98)	0.07	0.19
Smoker ever	Reference		
Smoker never	0.97 (0.78, 1.20)	-0.03	0.60
Smoking not known	1.20 (0.68, 2.11)	0.09	0.08
BMI <25	Reference		
BMI>= 25	0.99 (0.79, 1.23)	-0.02	0.74
BMI missing	0.33 (0.13, 0.83)	-0.01	0.91
Low BMI conditions	-	-	-
Structural gynaecology conditions	1.53 (0.49, 4.77)	0.04	0.47
Illegal opioid use	4.04 (0.56, 28.94)	-0.01	0.85
No NSAID use	Reference		
Non-selective NSAID use	1.19 (0.96, 1.48)	0.05	0.37
COX2 NSAIDs	0.95 (0.56, 1.59)	-0.01	0.82
Age	0.99 (0.98, 1.01)	0.11854	0.03*
Global test			0.31

* indicates which variables were included as time-varying covariates based on the Schoenfeld residuals test $ indicates the Pearson product-moment correlation between the scaled Schoenfeld residuals and log(time) for each covariate.

The unadjusted Cox regression for low libido is shown in Table 6-15. There appeared to be a relationship where long-term opioids were associated with a higher hazard of low libido as the hazard ratios were greater than 1 in all groups. However, the confidence intervals crossed through 1 and the results were not statistically significant. The Cox regression with adjustment (for pre-existing low libido, thyroid conditions, BMI, structural gynaecological conditions, illegal opioid use, smoking status, alcohol use, NSAID use and age as a time varying covariate) did not show a statistically significant relationship between opioid use and low libido, but the hazard ratio remained greater than one in all time periods except 1-2 years (see Table 6-15).

Table 6-15 Cox Regression adjusted and unadjusted for libido comparing duration of opioid use

Follow-up	Hazard ratio (95% CI) unadjusted	P	Hazard ratio (95% CI) adjusted	P
5 years	1.22 (0.99, 1.51)	0.06	1.19 (0.96, 1.48)	0.11
< 1 year	1.38 (0.94, 2.02)	0.10	1.35 (0.91, 2.01)	0.14
1-2 years	1.00 (0.66, 1.52)	0.99	0.89 (0.58, 1.37)	0.56
3-5 years	1.26 (0.92, 1.72)	0.15	1.18 (0.85, 1.62)	0.32

Cox regression was split for age over the five-year period and the hazard ratio was found to be statistically significant in 36-45 year olds with women who took long-term opioids having a higher hazard of being affected by low libido (Table 6-16). When the Cox regression over different age groups was adjusted (as described above) the hazard ratio remained significant in women 36-45 year-old (Table 6-16). The remaining age groups except in 46-55 year olds all had a hazard ratio over 1 but these were not statistically significant. This age group was then analysed over the three time periods and only remained statistically significant over the full five year follow-up and years three to five. The hazard ratios remained above 1 but the CI were wide, and following adjustment (as described above) the hazard ratio remained

statistically significant only over the whole five year follow-up (Table 6-16 and Table 6-17).

Table 6-16 Results of Cox regression for the outcome low libido and duration of opioid use comparing opioid duration split by age groups.

Age Range (years)	Hazard ratio (95% CI) unadjusted	P	Hazard ratio (95% CI) adjusted	P
18-25	1.14 (0.44, 2.96)	0.78	1.28 (0.47, 3.43)	0.63
26-35	1.16 (0.72, 1.87)	0.55	1.16 (0.71, 1.91)	0.56
36-45	1.69 (1.19, 2.40)	<0.001	1.64 (1.15, 2.35)	0.01
46-55	0.93 (0.67, 1.30)	0.67	0.89 (0.63, 1.26)	0.51

Table 6-17 Cox regression for low libido comparing opioid duration for 36-45 year olds unadjusted and adjusted

Follow-up	Hazard ratio (95% CI) unadjusted	P	Hazard ratio (95% CI) adjusted	P
5 years	1.69 (1.19, 2.40)	<0.001	1.64 (1.15, 2.35)	0.01
< 1 year	1.69 (0.91, 3.13)	0.10	1.76 (0.93, 3.32)	0.08
1-2 years	1.38 (0.68, 2.82)	0.37	1.27 (0.61, 2.64)	0.53
3-5 years	1.89 (1.11, 3.21)	0.02	1.78 (1.03, 3.07)	0.04

Overall the results for libido showed a relationship where the hazard of low libido seemed to be higher in women who took long-term opioids compared with women who took short-term opioids, however this difference did not reach statistical significance. The only age group with a statistically significant difference were women aged 36-45 years old and this relationship remained significant over the full five year follow-up period and in years 3-5 of follow-up.

6.4.3 Infertility

The proportional hazards assumption was tested using Schoenfeld residual test for the unadjusted Cox regression, the p value was 0.80 so the assumption was upheld. A log-log plot was also produced (Figure 6-7) the plots were very close together and appear to cross. A Kaplan-Meier curve (Figure 6-8) showed the two plots crossing early on and then the difference becoming wider with those not taking long-term opioids having a higher probability of infertility. The proportional hazards assumption was also checked for the adjusted Cox regression and this determined that NSAID use should be included in the model as a time varying covariate (see Table 6-18). The median follow-up time was 1268 days (IQR 597, 1825 days).

Figure 6-7 Log Log plot for infertility comparing duration of opioid use

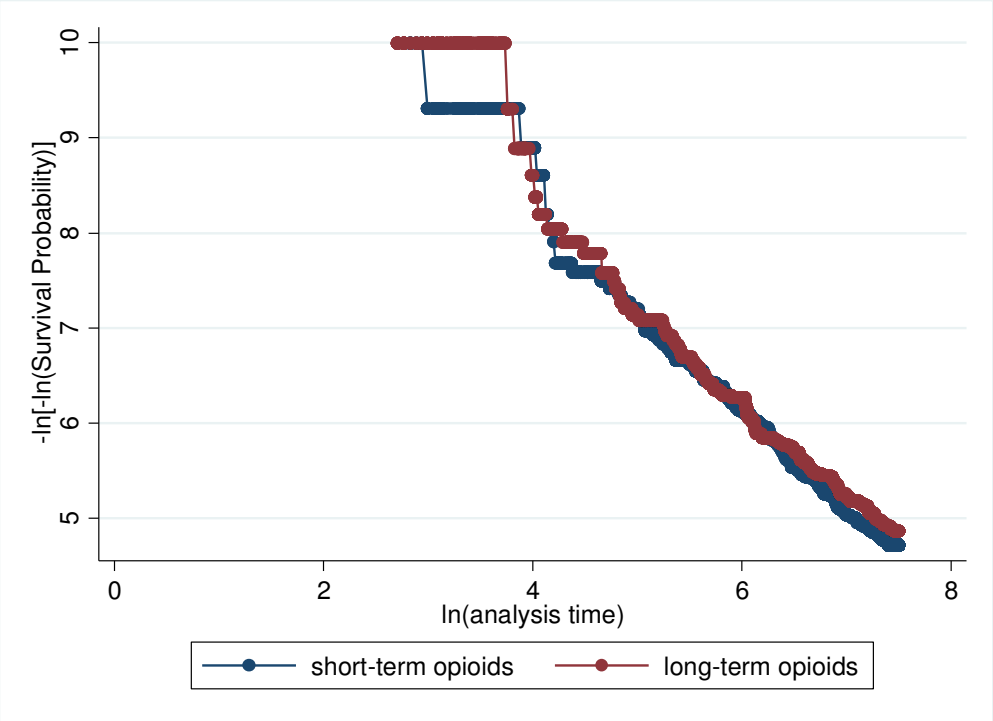


Figure 6-8 Kaplan-Meier curve for infertility comparing duration of opioid use

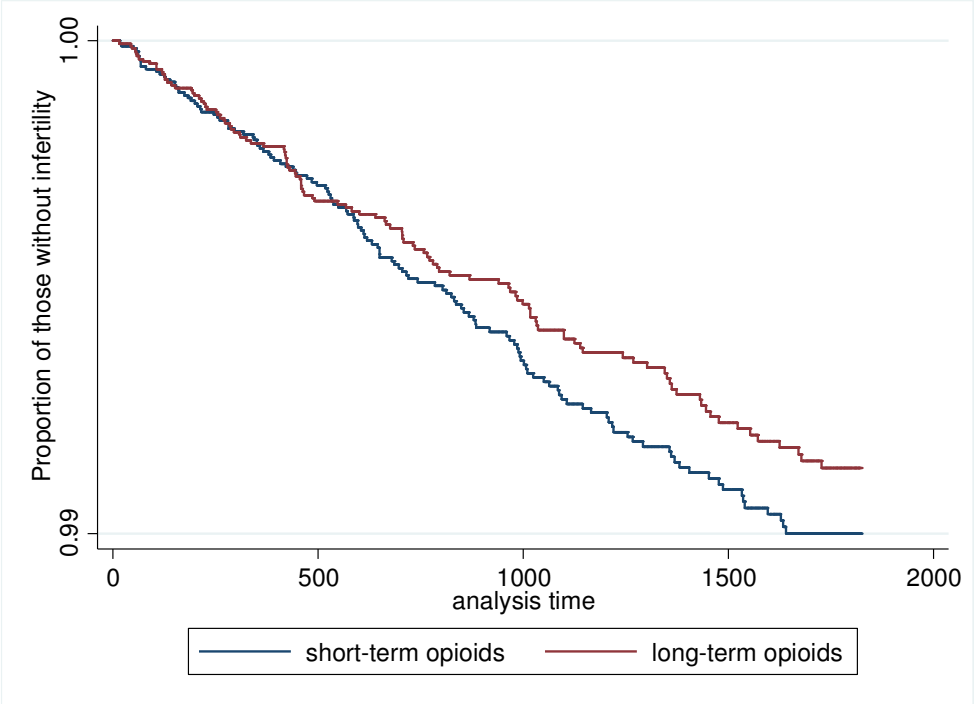


Table 6-18 Schoenfeld residuals testing the proportional hazards assumption for adjusted Cox regression for infertility and duration of opioid use

Variable	HR (95% CI)	Rho	P
Duration of opioid use	0.84 (0.65, 1.08)	-0.03	0.69
Pre-existing infertility disorders	23.16 (14.80, 36.23)	-0.09	0.13
Thyroid conditions (not specified hypo/hyper)	1.66 (0.23, 11.89)	0.05	0.42
Hypothyroid	0.59 (0.19, 1.85)	0.05	0.43
Hyperthyroid	-	-	-
Alcohol use ever	Reference		
Alcohol use never	1.04 (0.80, 1.34)	0.04	0.48
Alcohol use not known	0.66 (0.38, 1.13)	0.08	0.18
Smoker ever	Reference		
Smoker never	1.04 (0.80, 1.34)	-0.08	0.23
Smoking not known	1.31 (0.61, 2.81)	-0.00	1.0
BMI <25	Reference		
BMI>= 25	0.87 (0.67, 1.13)	-0.10	0.13
BMI missing	1.01 (0.58, 1.77)	-0.06	0.35
Low BMI conditions	-	-	-
Structural gynaecology conditions	2.35 (1.14, 4.84)	0.02	0.70
Illegal opioid use	-	-	-
No NSAID use	Reference		
Non-selective NSAID use	1.07 (0.83, 1.38)	0.13	0.04*
COX2 NSAIDs	1.21 (0.63, 2.33)	0.01	0.49
Age	0.91 (0.89, 0.92)	-0.07	0.46
Global test			0.46

* indicates which variables were included as time-varying covariates based on the Schoenfeld residuals test $ indicates the Pearson product-moment correlation between the scaled Schoenfeld residuals and log(time) for each covariate.

The Cox regression did not show any statistically significant difference between long-term and short-term opioid users and there was no uniform direction of change seen (see Table 6-19). When the results were adjusted for covariates (age, pre-existing infertility, thyroid conditions, BMI, structural gynaecological conditions, illegal opioid use, smoking status, alcohol use and NSAID use as a time varying covariate), the results of the Cox regression remained similar.

Table 6-19 Infertility Cox regression for duration of opioid use unadjusted and adjusted

Follow-up	Hazard ratio (95% CI) unadjusted	P	Hazard ratio (95% CI) adjusted	P
5 years	0.86 (0.67, 1.11)	0.25	0.84 (0.65, 1.08)	0.17
< 1 year	0.95 (0.61, 1.48)	0.82	0.94 (0.59, 1.48)	0.77
1-2 years	0.78 (0.49, 1.24)	0.29	0.76 (0.47, 1.23)	0.26
3-5 years	0.87 (0.59, 1.28)	0.47	0.82 (0.55, 1.23)	0.33

The Cox regression was then undertaken for each age group. This showed a hazard ratio of 0.61 (95% CI 0.39, 0.95) in the 36-45 year old age group which was statistically significant. The adjusted (as described above) Cox regression still found a statistically significant hazard ratio of less than 1 in women aged 36-45 years old, indicating a decreased risk of infertility in long-term opioid users see Table 6-20 for full results.

Table 6-20 Infertility Cox regression for duration of opioid use split for age categories unadjusted and adjusted

Age Range (years)	Hazard ratio (95% CI) unadjusted	P	Hazard ratio (95% CI) adjusted	P
18-25	1.42 (0.73, 2.75)	0.30	1.25 (0.61, 2.54)	0.54
26-35	0.88 (0.62, 1.24)	0.46	0.85 (0.60, 1.21)	0.36
36-45	0.61 (0.39, 0.95)	0.03	0.61 (0.38, 0.97)	0.04
46-55	No result		No result	

For this outcome there was no statistically significant difference seen between women taking long-term opioids and short-term opioids except in the 36-45 year old age group, which showed those women taking long-term opioids had a lower hazard of infertility than short-term opioid users. The hazard ratio was less than 1 in 36-45 year-olds over the full five year follow-up and this was statistically significant (Table 6-21).

Table 6-21 Cox regression infertility and duration of opioid use for age range 36-45 years unadjusted and adjusted

Follow-up	Hazard ratio (95% CI) unadjusted	P	Hazard ratio (95% CI) adjusted	P
5 years	0.61 (0.39, 0.95)	<0.05	0.58 (0.37, 0.92)	<0.05
< 1 year	0.55 (0.26, 1.20)	0.14	0.64 (0.29, 1.45)	0.29
1-2 years	0.81 (0.34, 1.97)	0.65	0.77 (0.31, 1.93)	0.57
3-5 years	0.55 (0.27, 1.11)	0.10	0.50 (0.24, 1.05)	0.07

6.4.4 Menopause

The proportional hazards assumption was tested using Schoenfeld residual test for the unadjusted Cox regression and p value (0.45) was not statistically significant, so the proportional hazards assumption was upheld for non-adjusted Cox regression. A log-log plot was also produced (Figure 6-10). The median follow-up time was 1144 days (IQR 536, 1825 days). A Kaplan-Meier curve is shown in figure 6-9 and this clearly indicated an increased number of events in the long-term opioid group. Each covariate to be included in the model was then tested individually and a Schoenfeld residual was undertaken on the entire model, a p value of 0.0 was found with four covariates contributing to this (pre-existing menopause symptoms, structural gynaecological disorders, age and NSAID use), these covariates were then included in the adjusted model as time varying covariates (see Table 6-22).

Figure 6-9 Kaplan-Meier curve for menopause comparing duration of opioid use

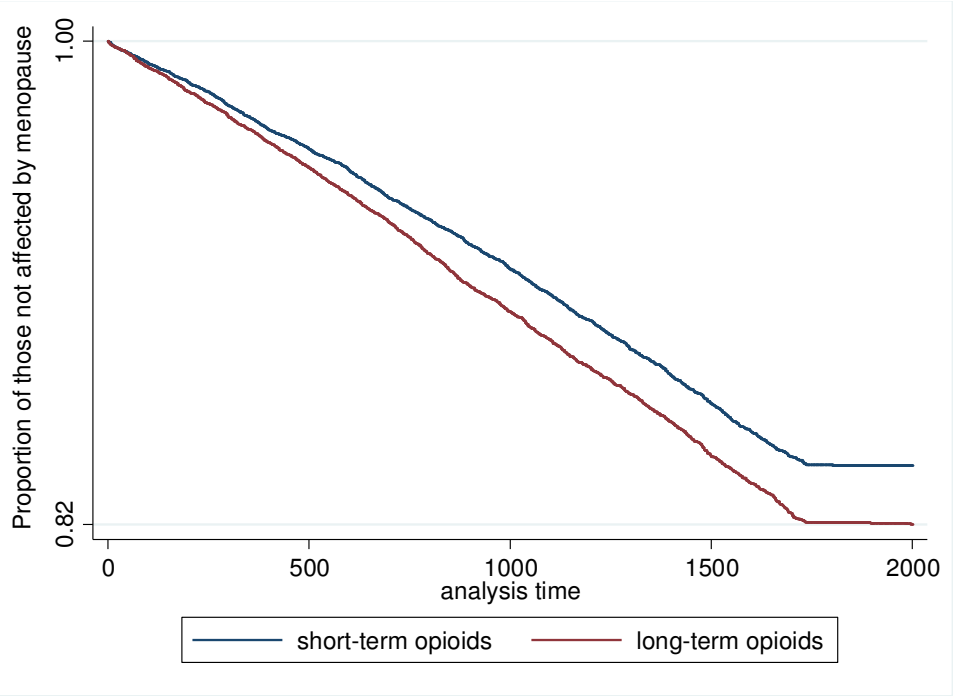


Figure 6-10 Log Log plot for menopause outcome comparing duration of opioid use

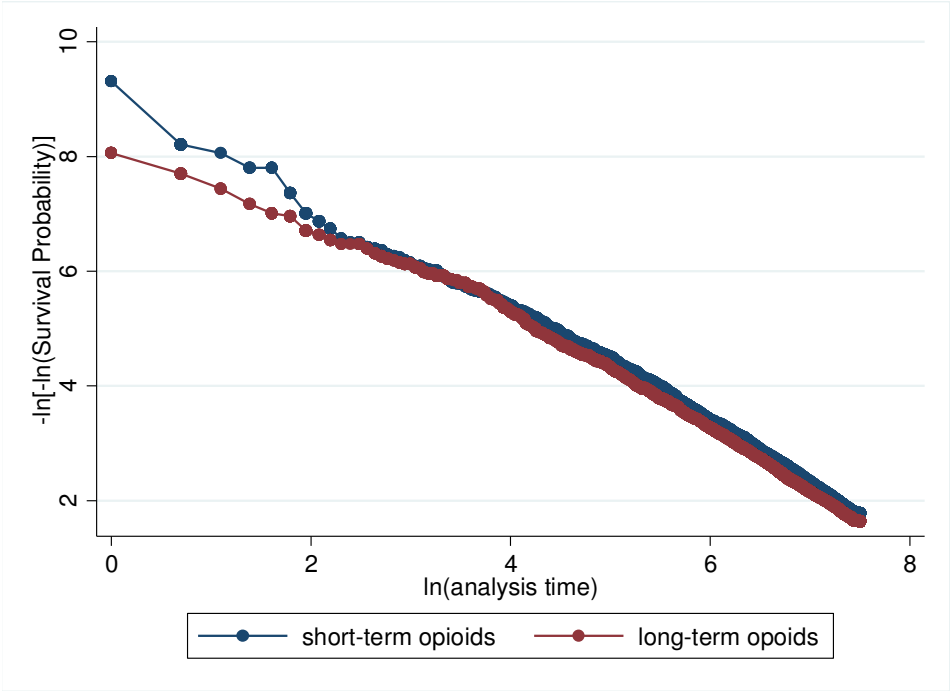


Table 6-22 Schoenfeld residuals testing the proportional hazards assumption for adjusted Cox regression for menopausal symptoms comparing duration of opioid use

Variable	HR (95% CI)	Rho	P value
Duration of opioid use	1.16 (1.10, 1.23)	-0.01	0.41
Pre-existing menopause disorders	2.09 (1.89, 2.31)	-0.08	0.00*
Thyroid conditions (not specified hypo/hyper)	0.95 (0.55, 1.64)	-0.02	0.10
Hypothyroid	1.01 0.85, 1.21)	-0.01	0.37
Hyperthyroid	0.57 (0.30, 1.10)	0.01	0.58
Alcohol use ever	Reference		
Alcohol use never	1.03 (0.94, 1.12)	-0.01	0.61
Alcohol use not known	0.92 (0.81, 1.11)	-0.01	0.54
Smoking ever	Reference		
Smoking never	1.09 (1.03, 1.16)	-0.02	0.20
Smoking not known	0.95 (0.81, 1.11)	0.02	0.12
BMI <25	Reference		
BMI>= 25	0.98 (0.93, 1.05)	0.01	0.56
BMI missing	0.77 (0.64, 0.92)	-0.01	0.33
Low BMI conditions	0.26 (0.04, 1.87)	-0.02	0.23
Structural gynaecology conditions	1.06 (0.66, 1.71)	-0.04	0.01*
Illegal opioid use	2.32 (0.96, 5.59)	0.02	0.20
No NSAID use	Reference		
Non-specific NSAID use	0.99 (0.74, 1.06)	0.26	0.07
COX2 NSAIDs	0.90 (0.79, 1.02)	-0.03	0.05*
Age	1.10 (1.09, 1.10)	-0.14	0.00*
Global test			0.00

* indicates which variables were included as time-varying covariates based on the Schoenfeld residuals test $ indicates the Pearson product-moment correlation between the scaled Schoenfeld residuals and log(time) for each covariate.

Cox regression for menopause consistently showed hazard ratios of 1.14 or more across the whole follow-up period and all of the time periods showed a statistically significant increased risk in long-term opioid users. The highest hazard ratio was seen in year two with a value of 1.19 (95% CI 1.06, 1.34) see Table 6-23 for full results. The Cox regression was adjusted (for thyroid conditions, BMI, illegal opioid use, smoking status, alcohol use and time varying covariates for NSAID use, pre-existing menopausal conditions, age and structural gynaecological conditions) and all time periods remained statistically significant see Table 6-23 for full results.

Table 6-23 Unadjusted and adjusted menopause Cox regression comparing duration of opioid use

Follow-up	Hazard ratio (95% CI) unadjusted	P	Hazard ratio (95% CI) adjusted	P
5 years	1.16 (1.10, 1.23)	<0.001	1.16 (1.10, 1.23)	<0.001
< 1 year	1.16 (1.04, 1.30)	0.01	1.16 (1.03, 1.30)	0.01
1-2 years	1.19 (1.06, 1.34)	<0.001	1.17 (1.04, 1.32)	0.01
3-5 years	1.14 (1.06, 1.24)	<0.001	1.16 (1.06, 1.25)	<0.001

The Cox regression was repeated for each individual age group (except those 25 years old and less where there were too few outcomes to undertake Cox regression). The hazard ratio was greater than 1 across all age groups and was statistically significant. The hazard ratio after adjustment (adjusted for thyroid condition, illegal opioid use, BMI, smoking status, alcohol use and the following time varying covariates age, NSAID use, pre-existing menopausal symptoms and structural gynaecological conditions) remained statistically significant in all age groups, see Table 6-24 for full results.

Table 6-24 Non adjusted and adjusted menopause Cox regression split for age categories comparing duration of opioid use

Age Range (years)	Hazard ratio (95% CI) unadjusted	P	Hazard ratio (95% CI) adjusted	
18-25	No results		No results	
26-35	2.09 (1.27, 3.43)	<0.001	2.00 (1.19, 3.34)	<0.001
36-45	1.35 (1.21, 1.50)	<0.001	1.32 (1.18, 1.48)	<0.001
46-55	1.09 (1.02, 1.17)	0.01	1.10 (1.02, 1.17)	0.01

Overall the results for menopause the hazard of reporting menopausal symptoms was higher in women taking long-term opioids than those receiving short-term opioids, this was a statistically significant change across the full five year follow-up and in all age groups.

6.4.5 Sensitivity analysis

Sensitivity analysis was undertaken using two methods. The first sensitivity analysis included only complete cases (cases with no missing data) and the second included only those without pre-existing reproductive dysfunction (defined in section 5.7). The results were similar with no change in statistical significance when the original analysis was compared with the sensitivity analyses, see Table 6-25 for the full results.

Table 6-25 Adjusted hazard ratios for complete cohort and sensitivity analysis including only complete cases and only those without pre-existing conditions comparing duration of opioid use (analyses including time varying covariates as described previously shown)

	All cases	Sensitivity Analysis (complete cases)	Sensitivity analysis (removed if pre-existing outcome condition)
Menstruation	1.14 (1.06, 1.22)	1.11 (1.01, 1.22)	1.12 (1.04, 1.20)
Libido	1.19 (0.96, 1.48)	1.26 (0.95, 1.68)	1.20 (0.97, 1.50)
Infertility	0.82 (0.64, 1.06)	0.80 (0.57, 1.12)	0.87 (0.67, 1.14)
Menopause	1.16 (1.10, 1.23)	1.15 (1.07, 1.22)	1.20 (1.13, 1.28)

6.5 Conclusion

This chapter has presented the results of the CPRD cohort study undertaken for this thesis. There was a significant increased hazard of both menopausal symptoms and abnormal menstruation in long-term opioid users when compared to short-term opioid users. The strengths and limitations of the cohort study will be discussed in the next chapter.

7 Cohort study discussion

The aim of the cohort study was to investigate the incidence of reproductive and sexual dysfunction in women prescribed opioids for potentially painful musculoskeletal conditions and the association between duration of opioid use and reproductive and sexual dysfunction. This chapter will summarise the findings of the cohort study, compare these results to what is already known and then discuss the strengths and limitations of the study. The chapter will then discuss the meaning of these results and how they might apply to the population of interest and the key messages from the study.

7.1 Summary of main findings

The cohort study described in chapters 5 and 6 found a statistically significant increased risk of menopausal symptoms and abnormal menstruation in women prescribed long-term opioids compared to those prescribed short-term opioids. This is the first study of its size to investigate this area and adds to an area where there has been previously little research (as seen in the systematic review in chapter 3). However, there was no increased risk of low libido or infertility found, although the number of women affected by low libido was much lower than that expected based on population estimates.

These results support the original hypothesis that long-term opioid use is associated with symptomatic disruption of the HPG axis.

7.2 Comparison with other studies

As discussed in Chapter 3, which reports the results of the systematic review, there were 12 papers (with 165 subjects investigated in total) investigating reproductive dysfunction in women aged 18-55 years old receiving long-term opioids. To the author's knowledge, there are no other studies that have used a large primary care cohort, or had the length of follow-up, as in the cohort study undertaken as part of this thesis. Previous papers all had small numbers, but they did show a trend towards an increased risk of HPG disruption in long-term opioid users, which agrees with the findings reported in Chapter 6. The results of the cohort study also fit with previous animal studies that have shown that long-term opioids are associated with decreased LH levels through several mechanisms which can lead to low levels of sex hormones (Vuong et al., 2010).

The cohort study found a statistically significant increased risk of abnormal menstruation in long-term opioid users. This is in agreement with the findings from the systematic review (section 3.5.1) and builds the evidence further, as only one of the studies in the systematic review found a statistically significant increased risk in opioid users in a small study. The studies in the review found a higher proportion of opioid users affected by abnormal menstruation (23-81%) in comparison with this cohort study (6.2%, 95% CI 5.9, 6.4%); this is likely due to the difference between database research (relying on medical records) and primary data collection research (Last, 1963). Medical records research only contains information if the patient has presented with a certain condition for medical care (this is known as the clinical iceberg and is discussed fully in section 4.6.1). The cohort study undertaken for this thesis also found an increased risk of menopausal symptoms in women prescribed

long-term opioids. This was not an outcome described in any of the studies in the systematic review, although it does fit with the hypothesis that long-term opioids disrupt the HPG axis (Daniell, 2008). A greater proportion of participants within the systematic review (61-100%) suffered with low libido compared with the cohort study (0.8% 95% CI 0.7, 0.9). Additionally, the number of women with a coded diagnosis of low libido was low in contrast to population estimates (25-41%) (Dunn et al., 1998; Laumann et al., 2005). This difference is likely due to the clinical iceberg and women not consulting their GP about problems with libido (due to a variety of reasons previously discussed), whereas they may reveal the condition on direct questioning (Last, 1963; Montgomery, 2008).

The cohort study was undertaken within a primary care setting which contrasts with the currently available literature mainly undertaken within secondary care (11/12 papers within the systematic review took place in secondary care clinics). This means that the study undertaken for this thesis is generalisable to the typical population using opioids in the UK for musculoskeletal pain (the majority of patients with chronic pain are treated in the community rather than in specialist clinics), whereas previous research may not be generalisable to a UK primary care population and as the numbers included were so limited may also not have been generalisable to patients with chronic pain treated with opioids in secondary care (Breivik et al., 2006).

The cohort study undertaken for this thesis adds to the previous research in this area as it was the first large scale cohort study to investigate reproductive and sexual dysfunction. The study is the first to find both an increased hazard of

menopause/menopausal symptoms and abnormal menstruation in women prescribed long-term opioids when compared to short-term opioids.

7.3 Strengths and limitations of the study

One of the major challenges during the design of the cohort study was addressing the issue of confounding by indication, which was discussed previously in section 4.7.3. A strength of the study was how confounding by indication was dealt with including matching during the recruitment stage. The two groups within the cohort were matched for date of opioid use and presence of a coded painful musculoskeletal condition. This meant all the participants across both short-term and long-term opioid groups were prescribed opioids and had a potentially painful musculoskeletal condition which the opioids were likely prescribed for, addressing important aspects of confounding by indication. Painful musculoskeletal conditions rather than CNCP were matched for, as they provided a more homogenous group of participants. However, this does mean that the results may not be generalisable to all CNCP patients. This method was unable to address confounding by severity (a subset of confounding by indication) or the longevity of the condition, which may then affect the duration of opioid use (Joffe and Rosenbaum, 1999). Long-term opioid users are more likely to have severe disease and this may mean they are prescribed opioids at a higher dose than short-term users. This could affect the results as daily morphine equivalent opioid dose was not taken into account within the cohort study and previous studies on adverse events have found increased risk of adverse events associated with increasing daily opioid dose (Bedson et al., 2019a; Saunders et al., 2009). There is evidence however, that the majority of long-term opioid users in the

UK are receiving less potent opioids, for example codeine 15mg and this is likely to be reflected in the cohort (Bedson et al., 2016).

The cohort study also considered all opioids as one so did not take into account different opioid types and this may potentially be a limitation. Some opioids may not have the same risk of adverse events as others, for instance buprenorphine seemed to have a fewer endocrine adverse effects than other opioids, which was highlighted by the systematic review in Chapter 3 and one study has also shown that tramadol has a lower risk of fractures when compared to hydrocodone (Solomon et al., 2010a). The nature of database research means that it cannot be guaranteed that the opioid was prescribed for the musculoskeletal condition (as the musculoskeletal condition and opioid were linked through a temporal association rather than a direct link in the database as this is not possible within CPRD) and this may introduce further confounding, as the indication for the opioid may be a different condition and this will affect the matching that was undertaken to build the cohort, however CPRD does ask for a code to be recorded when changing treatment regimen so this should help to link the opioid to a musculoskeletal condition (Jordan et al., 2006). Matching the cohort for opioid use ensured that all the women included were considered suitable for an opioid prescription and had no contraindications, which removed further potential systematic differences. The women in the short-term opioid group did not progress to long-term opioids and this may be due to many things including intolerance to the medicine, improvement in their condition or perception of increased risk associated with the opioid in some way. Consequently, systematic differences between the two groups may still remain, but compared to previous studies undertaken in this area this has been addressed as fully as possible.

One particular issue for this study is that CNCP is more likely to be present in the long-term opioid users as they are using long-term analgesics. CNCP can be conceptualized as chronic inescapable stress on the HPA (hypothalamic-pituitary-adrenal) axis, and stress can be a cause of HPG dysfunction and amenorrhoea (Blackburn-Munro 2001; The Practice Committee of the American Society for Reproductive Medicine 2008). CNCP can therefore be associated with the outcomes of interest and could not be matched for within the cohort study, which means there is likely to be residual confounding by indication. CNCP has been associated with low libido in previous work, with one questionnaire from chronic pain clinics showing 73% of patients (both sexes) reporting current sexual difficulties, compared with a survey of the general population which found 41% of women reporting sexual difficulties (Ambler et al., 2001; Dunn et al., 1998).

The comparison groups were matched for year of birth and this was important as age has a direct impact on two of the primary outcomes of the study (menopause and libido). Menopause becomes more likely as a woman gets older (the average age of the menopause is 52 years old in the UK) (Hardy and Kuh, 2005). Age has a direct link with menopause and it was important that this was taken into account during matching of the cohort (Hardy and Kuh, 2005). Age and menopausal status also have an effect on libido as both increasing age and being in the peri-menopause have been shown to be associated with low libido (Hayes et al., 2008). It was not possible to match for menopause as it was an outcome of interest but the cohort was matched for age by year of birth.

The category of opioid use was identified at the start of follow-up, whereby if a patient met the criteria for long-term opioid use at any point they were included as a long-

term user and if not as a short-term user. A long-term user may have stopped using opioids at any point during follow-up. Once assigned to a group, participants did not change groups, and this could be a potential limitation since in real life the opioid exposure would be time-varying, and this may have had an impact on the generalisability of the results. The identification of opioid users was based on prescriptions, but it cannot be established how or if the women were using the prescribed opioids. Identifying women purely as long-term or short-term users is also a potential limitation, as this is a binary measure and does not take into account different strengths, delivery methods and type of opioids that may be being used. In previous studies into adverse effects, the daily morphine equivalent dose has been measured, and in one particular study looking at fractures the increase in risk was only statistically significant in those that received 50mg or more of morphine equivalent per day (Saunders et al., 2009). Consequently, adverse effects may be dose dependent as well, but this was not part of the analysis within the cohort study (Bedson et al., 2019a; Saunders et al., 2009).

Type of opioid was also not considered and some opioids have different mechanisms of action when compared with other opioids; for example, buprenorphine, (previously discussed in section 2.3). This may have an effect on the risk of adverse effects associated with buprenorphine, since a previous review found that adverse effects occur at a lower rate with buprenorphine at therapeutic dose when compared with other opioids (Aloisi et al., 2009; Kress, 2009). Buprenorphine within therapeutic range appears to have a ceiling effect for adverse effects (including respiratory depression) and this may also be the case for endocrine adverse effects (Kress, 2009). Buprenorphine has been compared to morphine (equipotent doses in animal

studies) for immunosuppressive effects, however buprenorphine did not have an effect on the HPA axis whereas morphine caused an effect. There may be a similar effect for the HPG axis which is the area of interest to this thesis (Kress, 2009). Another study found that for fractures tramadol appeared to have a lower risk when compared to hydrocodone and all-cause mortality was higher for oxycodone and codeine compared to hydrocodone, so there may be variability between opioids for other adverse effects (Solomon et al., 2010a). All opioids were considered together for the purpose of the cohort study so this did not take into account the differences between opioids. Buprenorphine forms only a small proportion of opioid prescribing (<5%) based on the available evidence (Zin et al., 2014), therefore the inclusion of buprenorphine if it had a decreased risk of causing adverse effects may have only slightly weakened any association seen, whereas if the risk is lower for instance in those using tramadol this could have altered results more significantly as more patients will be taking this than buprenorphine (Kress, 2009; Zin et al., 2014). Buprenorphine can also be prescribed as a patch and the mode of delivery may also affect potential adverse events.

The setting of the study was important as it has both strengths and limitations. The cohort study was undertaken in CPRD a large primary care database within the UK (see section 4.61 and section 5.4). Using a database allowed investigation of the question in a large cohort with complete follow-up, allowing enough statistical power to undertake appropriate analysis. The sample should be representative of the population of interest and have good external validity, and CPRD has been shown to be broadly representative of the UK population when compared with census data (Herrett et al., 2010). This study is able to accurately represent the population using

opioids within the UK as it includes primary care patients (where the ongoing responsibility for prescribing most medicines within the UK lies), rather than just those seen in secondary care (where the majority of the current research has been undertaken) (NHS England, 2018; Wersocki et al., 2017). Only 23% of pain patients are seen by a pain specialist within the UK and these may represent a subset of patients with more severe pain (Breivik et al., 2006). CPRD has been validated for musculoskeletal conditions previously, one of the criteria for identifying the cohort. All prescriptions are recorded automatically within GP systems.

The identification of the cohort is unlikely to have missing or misleading data as both medicine and musculoskeletal pain are well documented in CPRD (Jordan et al., 2006; Lawson et al., 1998; Medicines and Healthcare products Regulatory Agency, 2009). In the UK, the only opioids available legally without prescription are low dose codeine and dihydrocodeine for a maximum of three days for acute injuries, so opioids used legally for any longer than this should be recorded within CPRD (Medicines and Healthcare products Regulatory Agency, 2009). All practices that contribute to CPRD have to meet data quality conditions and are regularly monitored, therefore the quality of data is high and this is reflected by the large number of validation studies that have been undertaken (Herrett et al., 2010, 2015). CPRD data is entered into medical systems contemporaneously for medical care and this means that it is not affected by recall or reporting bias. This is important for research into sensitive areas where social desirability may affect results (as in this case where sexual and reproductive function are being investigated) (Delgado-Rodriguez and Llorca, 2004). The participants were matched by general practice and this helps to limit the differences between practices and coding and inter-rater reliability should be

improved. This should mean that from each GP practice patients for both the short-term and long-term groups will have been identified in the same manner. Another advantage of using CPRD is that it allows the researcher access to information on relevant factors in the participants' past medical history and this can then be used in analysis of the data. Inevitably the data recorded within CPRD may not include factors which might be relevant to the analysis for this study.

Additionally, there are overall limitations that apply to all database research. As discussed previously, a lack of a coded diagnosis is considered as the absence of a disease but this is not necessarily the case (Herrett et al., 2015). Research in CPRD tends to have a high specificity but low sensitivity for identifying conditions so it is likely that all the participants identified as having a condition actually do have the condition, but there is a group of patients who represent false negatives (Herrett et al., 2010; Parikh et al., 2008). This inability to identify patients that do not present, but may still have a condition can be explained by a phenomenon described by Last (1963), who describes it as the clinical iceberg. The clinical iceberg is where only a small proportion of cases are actually seen by clinicians, and the rest remain hidden and medical services are not aware that they exist (Last, 1963). This means that a proportion of conditions are not recorded, but those that are, are clinically significant as patients have sought medical attention for them. It is important to consider that with sexual health conditions, this may also reflect that patients do not feel confident discussing these conditions with their doctor since they may be considered private, or patients may feel awkward discussing these issues, and consequently a larger proportion may not be reported (Delgado-Rodriguez and Llorca, 2004; Montgomery, 2008). This effect can be seen in the difference in low libido rates reported within the

cohort (less than 1%) and those expected in the general population from previous self-report studies (25-50%) (Dunn et al., 1998; Laumann et al., 2005). There is no reason to suspect that the effect of the clinical iceberg is different in the two arms of the cohort study. However, due to the low numbers of women reporting low libido there was not enough statistical power to show a significant difference even though long-term opioid users appeared to be affected more often.

Practices that contribute to CPRD do so on a voluntary basis and they tend to be larger practices. They may reflect a specific subset of high achieving practices, rather than be truly representative of all general practices, so when interpreting the results this needs to be considered (Campbell et al., 2013). It is also important to consider the limitation of recording (or ascertainment) bias where the patient may present with a condition, but this may not be Read Coded in the notes. There is evidence that only 85% of the issues discussed in consultations are recorded and only 37% of what is discussed is Read Coded (Salisbury et al., 2013). This does mean that patients may be presenting with conditions that they consider important but that these are then not recorded in the notes in a way that is accessible if using Read Codes to identify potential outcomes, so there is a possibility of missing further outcomes due to differences in recording between clinicians. Finally, it is important to note that CPRD has not been validated in previous studies for the outcomes of interest in this cohort study, so there is no evidence to suggest that CPRD is an appropriate method to investigate these conditions, although it does represent the best method available presently.

The cohort study took into account many important covariates during statistical analysis. NSAID use was included as a confounder within analysis as there is

evidence that short-term NSAID use is associated with a failure to ovulate. Although only prescribed NSAIDs were analysed, many NSAIDs (e.g. ibuprofen, aspirin) can be purchased over the counter in the UK and these would not be routinely recorded in the medical notes and consequently there effect could not be considered in this study (Salman et al., 2015). The cohort study was unable to take into account hormonal contraception (including intrauterine devices). Contraception can be obtained from family planning clinics in the UK, and this is information that is not recorded in CPRD. In the period from April 2012 to March 2013 1.2 million women attended family planning clinic for contraception and 47% received oral contraception which would not have been recorded in the GP records and accordingly would not be found in CPRD, there is no clear data regarding the number of times women consulted with GPs for oral contraception, but 7.7 million prescriptions were issued in 2012 for free of charge contraception (this would include prescriptions from both family planning clinics and GP) (Health and Social Care Information Centre, 2013; Prescribing and Medicines Team and Health and Social Care Information Centre, 2016)(Health & Social Care Information Centre 2013). Contraceptives can affect menstruation either through causing a withdrawal bleed each month (combined oral contraceptives), making menstruation heavier (copper coils) or potentially causing amenorrhoea (progesterone only pill, implants, progesterone intrauterine devices and depot injections). The combined oral contraceptive pill has been associated with decreased risk of premature ovarian failure and decreased sexual function (Chang et al., 2007; Davison et al., 2008). Contraceptive use could have affected the outcomes of interest, although there is no reason to suspect that contraception use would be different between the two groups.

Certain associated conditions were taken into account as they can cause several of the outcomes of interest. PCOS was included within the search for covariates, because PCOS accounts for 80% of cases of infertility due to anovulation. Patients with PCOS will often present with irregular or absent menstruation and this will be coded prior to a diagnosis. The number of comorbidities patients had was included in the analysis. This was calculated as a proxy measure as described previously based on the number of prescribed medicines, and it may over or underestimate the number of conditions. In the long-term opioid users there was a statistically significant increase in prescribed NSAIDs, compared with short-term users; this will have contributed to the number of comorbidities in this group of patients, as this was calculated based on number and type of medicines as described above (see section 5.8).

BMI is an important confounder, as it is a factor in both musculoskeletal conditions and menstrual disorders. Higher BMI has been directly associated with an increase in musculoskeletal disorders and worse recovery from these conditions which is linked to analgesics prescribing. BMI can also affect menstruation in women (if it is either high or low) (The Practice Committee of the American Society for Reproductive Medicine, 2008; Viester et al., 2013). There was BMI data available for 94.9% of the women within the cohort and this meant that it could be included in the statistical analysis, and a sensitivity analysis excluding those with missing data found similar results for each outcome in the cohort study. The cohort could also be adjusted for smoking and alcohol as the data was more complete than expected with over 90% of the participants having data available.

There is likely to be some residual confounding of which one aspect is that depression was not taken into account during the analysis. Depression and low mood are associated with worse pain, opioid use and also with low libido so this would be important to include in future studies, this was not included in the analysis of the cohort study so it is unclear whether this would have affected the results (Blackburn-Munro, 2001; Scherrer et al., 2014; The Practice Committee of the American Society for Reproductive Medicine, 2008).

Overall the strengths of the cohort study undertaken for this thesis, are that it is a large, longitudinal, cohort study with both matching and statistical analysis to control for confounding, which is an improvement on previous studies included within the systematic review. The main limitation of the study is that opioid use is considered at a single time point and did not take into account either dose or particular type of opioid used which may be important factors.

7.4 Meaning of the study and generalisability

To the authors knowledge this study is the first large scale cohort study to find that long-term opioids are associated with abnormal menstruation and menopausal symptoms in women aged 18-55 years old with musculoskeletal pain. These results are consistent with the previous limited evidence in this area, and build further on this as the first study to show an increased hazard of menopausal symptoms in long-term opioid users when compared with short-term opioid users. These findings are important for helping decision making surrounding opioid use and adds to the growing body of evidence surrounding the adverse effects of opioids (Els et al.,

2017b). The results of this study are important given the background of increasing opioid use for CNCP (Bedson et al., 2016).

This study is generalisable to women receiving long-term opioids in primary care for painful musculoskeletal problems, as CPRD is broadly representative of the UK population (Herrett et al., 2010). This is important as a large proportion of CNCP patients are treated in primary care and previous research has tended to focus on patients in secondary care (Breivik et al., 2006; Wersocki et al., 2017). This study focused on musculoskeletal pain, which is the commonest cause of CNCP in the UK, and the results are likely to be applicable to other causes of CNCP although further studies would be required to confirm this.

Opioid use should also be considered in the context of the patients' other problems, such as depression which can be independently related to opioid use, and the potential to become dependent on opioids as in those with a history of drug abuse.

The findings of this study should be considered when clinicians are prescribing and reviewing long-term opioids, and discussed with patients to improve shared decision making; discussing the risks and benefits prior to treatment with opioids is highlighted as important for good practice (Williams et al., 2013). Regular reviews of long-term opioids are recommended and clinicians should address potential sexual and reproductive dysfunction during these, as often patients may not raise these without the clinician asking directly (Montgomery, 2008; Williams et al., 2013).

7.5 Unanswered questions

There are a number of unanswered questions remaining following this study. The first set of questions are related to the opioid. Could the relationship observed in this

study be affected by opioid dose, type, or mode of delivery (patches or oral therapy)? Is there a safe daily dose of opioids in order to minimise the risk of associated reproductive dysfunction? This could be addressed by adjusting or stratifying for daily morphine equivalent dose in further studies, and taking into account the route of opioid, or type of opioid used (e.g. buprenorphine vs. morphine). This could help to improve decision making related to the level of risk associated with using opioids, and what dose and mode of delivery may carry the lowest risk. Another question that needs to be addressed is whether the symptoms of reproductive and sexual dysfunction resolve on withdrawal of the opioid, this would need to be examined as a longitudinal study where patients were followed up after stopping opioids

The study did not include depression as a possible confounder and it would be important to look at the role that depression may play, as there is clearly a complex relationship as depression can be related to CNCP (in this case pain secondary to musculoskeletal conditions), opioid use itself, and sexual dysfunction.

The cohort study found a lower prevalence of low libido compared to the prevalence expected in the general population, and this discrepancy deserves further investigation. It is important to understand whether this reflects the actual levels of low libido in this population or if it is due to the nature of database research. One way to address this question would be to undertake a self-report study of women and ask about sexual function directly.

Another area where future research may focus is examining the use of hormonal assays for investigating how levels of hormones may be affected by opioids. This information could be used to identify early problems in reproductive function.

It may also be important in the future to understand how women feel about reproductive dysfunction as a potential opioid adverse effect and where their priorities might lie during treatment. If a woman experienced adverse effects but was achieving good pain relief with their opioid analgesic, what would be a priority in terms of ongoing treatment? Qualitative research in this area would help us to better understand patients and doctors priorities.

7.6 Key messages

- Long-term opioid use is associated with a higher risk of menopause and abnormal menstruation than short-term opioid use. This is important to consider when initiating the prescription of opioids and also when undertaking medicine reviews.
- Risk is higher in younger women receiving long-term opioids compared with short-term users but the actual numbers affected are low.
- The prevalence of low libido was lower in the cohort than expected and this requires further investigation.

7.7 Conclusion

This cohort study supports the hypothesis that women taking long-term opioids are at higher risk of developing symptoms of HPG axis disruption than those who have taken short-term opioids. This substantially extends the body of evidence that show opioids are linked to reproductive and sexual dysfunction. This is an important possible adverse effect with opioid treatment and it should be discussed with women commencing long-term opioids as it may affect their decision making process. It will be important during initiation of opioids that these possible adverse effects are

discussed and then screened for at medicine reviews. The study found low numbers of women with low libido recorded in their electronic records; if women were informed that this was a potential adverse effect, they may be more likely to report it. The results of the cohort study add to the growing body of evidence that opioids carry significant potential adverse effects and this should be balanced with the lack of evidence for their effectiveness in CNCP.

8 Cross-sectional study methods

This cross-sectional study was undertaken to investigate the potential relationship between opioid use and female sexual dysfunction (FSD) further. A cross-sectional study was chosen, as the CPRD cohort study found less than 1% of the cohort had a coded diagnosis of low libido, whereas population estimates are much higher, with previous studies finding 73% of patients with chronic pain and 41% of women in the general population reporting sexual dysfunction when surveyed, the systematic review also found 61-100% of those studies reported sexual dysfunction (Ambler et al., 2001; Dunn et al., 1998; McCool et al., 2016). A cross-sectional study can investigate this area more directly than the cohort study and gain information from women that they may not necessarily have discussed with their GP and therefore would not be recorded in the database (Last, 1963; Montgomery, 2008). Self-report cross-sectional studies have been found to be useful for investigating sensitive subjects and this was discussed in section 4.4.2. This chapter will discuss the methods for the cross-sectional study undertaken for this thesis.

8.1 Summary

This study was undertaken as a cross-sectional postal survey of women aged 18-45 years old with a potentially painful musculoskeletal condition and a prescribed opioid. Quantitative data was collected using a single self-report postal questionnaire, and if the participant consented, from a review of the medical records. The main outcome of interest was FSD and this was assessed via the cross-sectional questionnaire.

8.2 Aim

The primary aim of this study was to investigate associations between opioid use and FSD in women with musculoskeletal conditions using a cross-sectional study.

8.2.1 Objectives

1) To investigate the prevalence of FSD in women aged 18-45 years old receiving opioids for musculoskeletal pain.
2) To compare the prevalence of FSD in women currently using opioids with the prevalence of FSD in women who have used opioids in the past but are no longer using opioids.
3) To compare the number of women with FSD according to total morphine equivalent daily dose.
4) To compare self-reported rates of FSD with those recorded in the medical records.

8.3 Ethical Approval

This study was approved by the West of Scotland research ethics service (reference number 17/WS/0182). The approval letter is included as Appendix 15. The study was also approved by the Health Research Authority. A single minor amendment was approved to increase the number of General Practices included from 20 to 30. The ethical approval application was undertaken by ER.

8.4 Setting

Participants were recruited from 30 General Practices within the NIHR West Midlands Clinical Research Network (WM:CRN).

8.5 Sample size

The sample size calculation was based on unpublished data, from a postal questionnaire by Dunn et al (1998, unpublished data available from the author on request). This data showed an odds ratio for sexual dysfunction of 2.2, when comparing those taking opioids to those without opioids (31% of those receiving opioids reported sexual dysfunction compared with 17% of those not using opioids). A two-sided 95% significance level, a power of 80%, and a ratio of 1:1 for comparison groups were used. The calculation estimated a sample size of 316 women. The study described above, had a response rate of 49% in women of all ages, but the response rate in those less than 57 years of age was 43% (Dunn et al., 1998). Sensitive topics are widely believed to cause a lower response rate; a Cochrane review found an odds ratio for response of 0.94 (95% CI 0.88, 1.0) when sensitive questions were included compared with non-sensitive questions (Edwards et al., 2009). Based on the sample size calculation of 316 and an expected response rate of 43%, 735 women would need to be invited. However, it was felt that it was likely that the response rate would be lower, due to decreasing participation rates in postal surveys, the sensitive nature of the study and the age range of participants being lower than the sample returning a 43% response rate (Galea and Tracy, 2007). The national census, which has excellent response rates, had a response rate of 88% in women aged 20-24 years old which is 10% less than the response rate of 98% in women aged 60-64 years old; if this 10% decrease in response rate is taken into account the study required 957 women to be invited, which was adjusted to 1000 (Office for National Statistics, 2015). Therefore, an estimated 1000 women were invited to participate in order to achieve a sample size of 316.

8.6 Study population

Participants were women aged 18-45 years old who were registered with a GP and had a coded potentially painful musculoskeletal condition who had recently been prescribed opioids.

8.6.1 Inclusion Criteria

- Women
- Aged 18-45 years old at the time of prescription. This age range was chosen based on previous studies which have shown the average age of the natural menopause in the UK to be 52 years and 11 months, with initial symptoms noticed at 50 years and 10 month (Hardy and Kuh, 2005). Sexual dysfunction has been shown to increase through the peri-menopause so the age was restricted in order to decrease the chance of women with menopausal symptoms being included in the study (Gracia et al., 2004).
- Prescription of an opioid from group three (e.g. codeine 15mg), group four (e.g. codeine 30mg) or group five (e.g. oxycodone, morphine) within the six months prior to records search. These groups represent moderate to very strong opioids, based on a previously developed consensus model of hierarchically arranged equipotent analgesics including opioids (Bedson et al., 2010). This was discussed in section 2.3 and the model is shown in figure 2.1.
- A potentially painful musculoskeletal condition coded within the six months prior to medical records search

8.6.2 Exclusion Criteria

- Symptoms and signs which indicated a serious pathology (cancer diagnosis) or red flag conditions that required urgent medical attention (e.g. fractures, cauda equina, and septic arthritis).
- Inflammatory joint condition (e.g. rheumatoid arthritis or gout)
- Inability to read and speak English
- Vulnerable patients (assessed by GP), including patients on the QoF mental health or learning disabilities register
- Pregnant
- Current hormone replacement therapy (HRT) use
- Menopause

8.6.3 Identification of study population

The study population was identified through Read Code searches at each participating practice. The Read Codes for the search were developed in partnership with the WM:CRN who have extensive experience of searching primary care records. The search was adapted from previous searches used for studies within the Research Institute for Primary Care and Health Sciences at Keele University. The opioid analgesic search was taken from the Keele University's STAMP study (Smartphone and Tablet Application for Medicines and Pain) (Bedson et al., 2019b). The musculoskeletal search terms were a combination of codes used in STAMP and in KAPS (Keele Aches and Pains Study also undertaken by Keele University) (Campbell et al., 2016) which were used to identify potentially painful musculoskeletal conditions, with any codes relating to menopause or traumatic injuries removed. The WM:CRN have pre-made code lists for certain exclusion

criteria including identifying vulnerable patients, these were reviewed by ER prior to use in the search. The majority of the exclusion criteria were identified on an as 'ever' occurred basis, except fractures where exclusion only occurred if the fracture was within the 12 months prior to the search to identify participants. The average healing time for fractures is between two and four months depending on the location and type of fracture, allowing an exclusion period of 12 months meant that participants should have recovered from any fractures prior to the start of six month identification period (Solomon et al., 2010b). An example of the codes used for the search can be found in Appendix 12.

8.7 Questionnaire construction

Where possible validated measures were identified and used.

8.7.1 Assessing female sexual dysfunction (FSD)

A literature review was undertaken to find an appropriate tool to use in order to identify women with FSD. Identification of FSD is complicated through the use of multiple classification systems as described previously (section 2.5.1), and depending on the classification system used, the tools assess slightly different things. Over 40 tools were identified. The most relevant tools are shown in Table 8-1. The most widely used and validated tool is the female sexual function index (FSFI); however this was developed for assessing severity of FSD that had previously been diagnosed, not for the initial identification of FSD (Rosen et al., 2000). Several tools have been validated against the FSFI for identification of women with sexual dysfunction. One of these tools is the STEFFI (full version), which has shorter versions the STEFFI-1, STEFFI-2 and STEFFI-5 (STEFFI is not an acronym, the tool

is named after the common German girls name), originally validated in the German language against the FSFI. The STEFFI-5 had 83.1% sensitivity and 81.2% specificity for identifying FSD when compared with the FSFI, and this tool has been translated into English (Kriston et al., 2010). The STEFFI tool does not require the woman to be in a sexual relationship; this was important since the tool needed to be applicable to women who might not currently be in such a relationship. The percentage of women identifying themselves as single in the most recent UK census was 34.6% of those aged over 16 years old, with this percentage decreasing with age. However, identifying as single does not mean that a person is not sexually active (Office for National Statistics, 2016). STEFFI also includes an important question regarding whether the participant is satisfied with their sex life because definitions for FSD now include the woman being distressed due to symptoms rather than symptoms in isolation (American Psychiatric Society, 2013; Basson et al., 2001; McCabe et al., 2016; World Health Organisation, 2012). The Arizona Sexuality Experience Scale (ASEX) had a similar sensitivity (82%) and specificity (90%) and was also considered as the measure of choice for the final questionnaire (McGahuey et al., 2000). The main drawback with ASEX is that it was developed for use in people on psychotropic medicines and has not been validated outside of this population.

STEFFI-5 and ASEX were both discussed with a patient and public involvement and engagement (PPIE) group and it was felt that both would be acceptable measures from a participant's point of view (see section 8.11). STEFFI was chosen as it asks about sexual function overall as well as specific symptoms, and it provides a more comprehensive assessment of sexual function (12 questions vs. 5). This is important

as FSD is the primary outcome of the study. Another positive factor for using the STEFFI-5 was that it looks at sexual function over the previous six months which is in line with the identification of participants for the study (opioid use within the previous six months and a painful musculoskeletal condition). STEFFI-5 consists of five questions. Each question scores either one or zero depending on response and adds to a total between zero and five. Scores of three or more should be considered positive for FSD whereas scores of two or less should be considered as a negative test. No license is required for use of STEFFI-5 and it is freely available for use if cited (Kriston et al., 2010).

Table 8-1 Tools to assess female sexual function

Tool	Population	Time scale	Administration and time to complete	Requires partner	Scale	Validation	Is distress assessed?
Arizona Sexuality Experience Scale (ASEX) (McGahuey et al., 2000)	Developed for patients taking psychotropic drugs	Past week	Self or clinician administered		5 item scale to assess five major aspects of FSD	Cronbach's alpha = 0.9055. ROC AUC 0.9292 +/- 0.29. Sensitivity 82%, specificity 90%, PPV 88%, NPV 85%.	No
Brief index of sexual function for women (BISF-W) (Mazer et al., 2000)	Partner status strongly affects results	Past month	Self-administered 15-20 minutes	No but affects results	22 item scale to assess 7 domains	Cronbach's alpha overall = 0.70 Domains 1=0.72, 2=0.39, 4=0.45, 5=0.72, 6=0.61, 7=0.08	No, asks about satisfaction rather than distress
Brief profile of female sexual function (B-PFSF) (Rust et al., 2007)	Postmenopausal women who are experiencing low sexual desire	2-3 months	Self-administered		7 item	Cronbach's alpha 0.8, ROC AUC 0.99	Yes
Deragotis Sexual Function Inventory (Derogatis, 1997)	All women	4 weeks	Self-administered 45 minutes		245 items	Cronbach's alpha 0.8, PPV 75%.	Yes
Decreased Sexual Desire Screener	Any age	No time frame given	Non expert administration 5 minutes		4 or 5 item scale	4 item scale sensitivity 88.4, specificity 77.5	Yes

Tool	Population	Time scale	Administration and time to complete	Requires partner	Scale	Validation	Is distress assessed?
(DSDS) (Clayton et al., 2009)						5 item scale sensitivity 83.6, specificity 87.8	
Female Sexual Dysfunction Scale (FSDS) (Derogatis et al., 2002)	Any age for measuring distress in women with FSD	No time frame	Self-administered 5-10 minutes	No	12 items	Sensitivity 88%, Specificity 93%	No
Female Sexual Function Index (FSFI) (Rosen et al., 2000)	Heterosexual women with FSD to establish severity	4 weeks	Self-administered 15 minutes	Yes	19 item scale 6 domains	Cronbach's alpha 0.85-0.95	No, measures satisfaction
Keele Sexual Relationships Questionnaire (SeRQ) (Dunn et al., 1998)	Women	3 months	Self-administered	No	15 item scale	Not given	No, measures satisfaction
Natsal-SF: A Measure of sexual function for community surveys (Mitchell et al., 2012)	Women of any age who have had sex in the past year	Past year	Interviewer administered	Yes	17 items	Comparative fit index = 0.963. Developed so that male and female sexual function could be tested with the same model.	Yes
Profile of	Post-	4 weeks	Self-	Yes	37 item	Cronbach's alpha	Yes

Tool	Population	Time scale	Administration and time to complete	Requires partner	Scale	Validation	Is distress assessed?
Female Sexual Function (PFSF) (McHorney et al., 2004)	menopausal females		administered ?time to complete as not reported		scale 7 domains	0.74-0.96	
Sexual interest and desire inventory female (SIDI-F) (Clayton et al., 2006)	Pre-menopausal women with hypoactive sexual desire dysfunction (HSDD) to measure response to treatment	4 weeks	Clinician administered tool Time to administer not reported	Yes	13 item scale 5 domains	Cronbach's alpha 0.79 in European women	Yes
Sexual function questionnaire (SFQ) (Quirk et al., 2002)	For use in pharmacological clinical trials	4 weeks	20 minutes	Yes	26 items 7 domains	Cronbach's alpha 0.70-0.91	No satisfaction assessed
STEFFI (not an abbreviation) (Kriston et al., 2010)	Any age women	6 months	1 minute- 10 minutes	No	1 item, 2 items, 5 items and 12 items respectively	4 versions: STEFFI-1 (sensitivity 76.4, specificity 76.5), STEFFI-2 (sensitivity 93.5, specificity 60.1), STEFFI-5 (sensitivity 83.1%, specificity 81.2%)	Yes

Tool	Population	Time scale	Administration and time to complete	Requires partner	Scale	Validation	Is distress assessed?
						and STEFFI	

8.7.2 Medicine use

There is a lack of validated questionnaires for self-reported medicine use. The majority of measures focus on adherence to prescribed medicine rather than identifying medicines currently in use (Garfield et al., 2011; Svarstad et al., 1999). Willeboordse et al developed a medicine use questionnaire for use in patients over 65 years old to aid in medicine reviews, which they compared to a medicine history gained through non clinician interview (Willeboordse et al., 2016). Reported medicines were compared between the self-completed questionnaire and the interview and this found an 87.6% (95% CI 84.7, 90.5%) agreement. Agreement was affected by health literacy, with agreement in those with low health literacy being 83.5 % (95% CI 76.7, 90.4%), and by number of medicines, with those taking more than 10 medicines agreeing between the two methods for 78.4% (95% CI 71.9, 84.9%) of medicines. Agreement for the entire medicine list was much lower at 45.4% (95% CI 35.8, 55.3%) and this was similarly affected by health literacy and number of medicines (Willeboordse et al., 2016). The first section of this tool asks questions around specific medicines and then about adherence to medicines. These tools were used as a basis for developing the medicine use section of the current questionnaire and this development process received input and final approval from PPIE. It was important that the tool included enough information to be able to calculate the daily oral morphine equivalent dose in order for this to be used in the analysis of this data. Where the participant consented to records review, this was used to replace any missing items from the questionnaire for medicine use. This was particularly important for the dose and name of opioid prescribed. The information was used in a sensitivity analysis. It was also important to determine which analgesics participants

might have used within the past six months, including any opioids. The question in the survey asked specifically about any medicine used for pain within the last six months but not currently being used, including the reasons for stopping these medicines.

Comparison measures were undertaken comparing total daily morphine equivalent doses with ≥20mg/day as the cut off between high and low doses within current opioids users, this cut off has been used in previous studies investigating opioid use so should keep the results in line with data on adverse effects that is already available (the method for calculating morphine equivalent dose is explained in section 8.13) (Dunn et al., 2010). Duration of opioid use was also collected for those currently using opioids.

Data on analgesics other than opioids was collected. Non-opioid analgesics were split during data analysis by ER into NSAIDs, Paracetamol, Gabapentoids (pregabalin and gabapentin both recommended by NICE for neuropathic pain) and antidepressants used for pain. Antidepressants for pain included any antidepressant the patient indicated was used for pain relief and the specific antidepressants amitriptyline and duloxetine were included if they were recorded in the current medicine section rather than the analgesics section of the questionnaire. Amitriptyline and duloxetine are the only antidepressants recommend for neuropathic pain in primary care by NICE (National Institute for Health Care and Exellence, 2013).

Contraception was addressed separately to other medicines, as this can be delivered in many ways other than a tablet form. This may mean that an implant for instance would not be reported as a medicine. A recent study comparing self-report to objective assessment found that asking the simple questions “are you using a

contraception method" and "what method are you using" produced 100% sensitivity and specificity (Smith et al., 2018). A single question was used to assess contraception based on this, with a tick box list for methods of contraception, including no contraception. This method allowed for the participant to indicate they were using either no contraception or more than one method since it was important to get accurate information on hormonal contraceptives currently being used to include within the analysis.

Information was also collected from patients on all other medicines they had used within the previous four weeks, this included prescription and over-the-counter medicine. The dose of these medicines or the frequency of use was not requested as this information was not needed to calculate a daily dose and this decreased respondent burden from the survey.

8.7.3 Pain

The presence or absence of chronic pain was important to assess as part of the questionnaire, so it could be included in analysis as a confounding factor. Pain can be assessed in a wide variety of ways. The particular tool used depends on several factors, including if a measure of change is needed or a single time point, and the specific condition being investigated (Hawker et al., 2011). The SF-12 contains a single item for assessing pain, but this does not assess level of pain or frequency of pain, and therefore was inadequate to assess current pain (Jenkinson and Layte, 1997). The chronic pain grade questionnaire was developed by Von Korff et al (1992) and has been validated for use in UK postal questionnaires (Von Korff et al., 1992; Smith et al., 1997). The positive features of the chronic pain grade questionnaire are that it assesses current pain and over the previous six months, which for this study

was useful given that women will have been identified as having a painful condition within the last six months and this may not still be present. The tool gives a grade from zero to four based on pain intensity (from questions one to three) and disability points (disability score from questions five to seven plus the answer from question four). A zero grading equates to no pain, and grade four indicates the highest disability possible due to pain (see Table 8-2). The chronic pain grade has been validated for use in UK postal questionnaires through comparison with the SF-36, has a Cronbach's alpha of >0.9, and item-total correlations of >0.68 for all items indicating good internal consistency and reliability (Smith et al., 1997). No license is needed for use of the Chronic Pain Grade questionnaire.

Table 8-2 Chronic pain grade classification (Von Korff et al., 1992)

Grade	Pain intensity (0-100)	Disability points
0	0	0
1	<50	<3
2	≥50	<3
3	Any	3 or 4
4	Any	5 or 6

8.7.4 Psychological wellbeing

PHQ-2 has been validated for use in primary care settings for identifying depression (Arroll et al., 2010; Löwe et al., 2005). PHQ-2 is a two question item with a four point Likert scale for response for each item (Löwe et al., 2005). The participant was also asked if they have ever been diagnosed with depression or anxiety in the medical conditions section of the questionnaire. The short form health survey (SF-12) also

calculates a mental component score (MCS) that is a measure of psychological wellbeing; this is discussed fully in section 8.7.5.

8.7.5 Health and wellbeing

There are many validated measures for health related wellbeing (Busija et al., 2011). The SF-36 is a widely used tool to assess health related quality of life (HRQoL), which aims to measure “general health concepts not specific to any age, disease or treatment groups” (Ware and Sherbourne, 1992). The SF-36 assesses eight domains, with four measuring physical functioning and four measuring mental functioning. The eight domains are as follows i) limitations in physical activities because of health problems, ii) limitations in social activities because of physical or emotional problems, iii) limitations in usual role activities because of physical health problems, iv) bodily pain, v) general mental health (psychological distress and well-being) vi) limitations in usual role activities because of emotional problems, vii) vitality (energy and fatigue) and viii) general health perceptions (Ware and Sherbourne, 1992). The SF36v2 takes around ten minutes to complete. The SF12v2 assesses the same eight domains but has one or two questions only per domain and this decreases the time burden in completing it to under three minutes. Both of these measures are suitable for use in the general population as well as in patients with clinical diagnoses (Busija et al., 2011). The SF-36 is more accurate for considering individual domains whereas the SF-12 and SF-36 are comparable if physical component summary (PCS) and mental component summary (MCS) are the main outcomes (Busija et al., 2011). Both have been validated internationally and shown to be comparable (Gandek et al., 1998). They are available in four week recall and one week recall forms. In studies the SF-12 often contains less missing data than the SF-

36 with the SF-12 having at least one missing item in 9.6% of responses and the SF-36 in 26% of responses (Loge et al., 1998; Perneger and Burnand, 2005). The SF-12 was chosen in preference to the SF-36 due to the lower number of responses affected by missing items, and decreased respondent burden, despite the decreased accuracy for assessing individual domains. When the SF-12 calculates PCS and MCS domain scores even a single missing value in each domain will return an invalid score, although imputation techniques can be used to overcome this (Liu et al., 2005). The SF-36 has been assessed for readability using Flesch-Kincaid Grade Level and found to have a mean grade level of 6.4 or median level of 4.8 consistent with easy and very easy reading levels. However, 36% of items scored above 9.5 indicating the participants need reading levels equivalent to those in high school (Calderón et al., 2006). The required license agreement (#CT184958 OP059432) has been agreed for use of the SF-12 in this study (see appendix 14).

8.7.6 Physical health

BMI was calculated from self-reported height and weight if provided preferentially over BMI recorded in the notes, as it was more likely to be up to date (there is evidence that BMI within CPRD which is analogous to GP records is often out of date) (Bhaskaran et al., 2013). There was an option for the participant to report their height and weight in metric, or imperial units and the database was built to accommodate this. Where there was missing data and consent for medical records review, the most recent height, weight and BMI were used from the participant's medical records in the sensitivity analysis.

Smoking status (five options: never smoked, ex-smoker, and current smoker split into ≤10, 11-20 and ≥21 cigarettes/day), alcohol use (split by frequency of alcohol use

daily, once or twice a week, once or twice a month, once or twice a year and never) and illicit drug use (yes or no response, with a free text box for which illicit drugs if answering yes) were included within the demographics section as simple tick box questions.

The participants were also asked for specific self-reported health conditions, including anxiety, chronic pain, depression, menopause, joint pain, endometriosis, chronic pelvic pain. Menopause and pregnancy were excluded from the study during identification of participants, but menopause was included in the questionnaire, as women may not have presented to their GP with menopausal symptoms, so may still have been included in the study at the search stage, whereas pregnancy is likely to be recorded on the GP system so was not included in the questionnaire (Last, 1963). Endometriosis and chronic pelvic pain were important as these are both possible confounders that can affect a woman's sexual function and also indications for analgesic use (Pluchino et al., 2016).

8.7.7 Demographics

In order to describe the sample demographics questions on age, ethnicity, marital status, children and whether the participant lived alone were included. Age was self-reported. However data from the original search which includes date of birth allowed us to compare the ages of responders and non-responders. Index of multiple deprivation for each participant based on the practice postcode they were registered with was also calculated. This gives a rating on a scale of 1 (most deprived) to 32,844 (least deprived) and takes into account income, employment, education and skills, health, crime, barriers to housing and living environment and is based on census data (Department for Communities and Local Government, 2015a, 2015b).

Index of multiple deprivation for responders and non-responders was calculated and compared.

The composition of the full survey instrument in shown in Table 8-3.

8.7.8 Reading age

As discussed in Section 4.4.5, it is important when designing a self-report questionnaire to aim for a reading level of between 8 and 10 years-old, or five years of education. Certain parts of the questionnaire are made up of pre-validated measures and as such the reading age of these sections could not be altered. The three sections that were designed specifically for this questionnaire (Sections 2, 3 and 6) all have a reading ease of less than 10 years old (see Table 8-4) if using Flesch-Kincaid which is appropriate based on the guidelines for medical information. Readability was calculated using Word 2013 (Microsoft, 2013a).

Table 8-3 Sections within the postal questionnaire and the instruments used to assess each area

Section	Measure/tool	Categories	Number of items
1 - Pain	Chronic pain grade (Von Korff et al., 1992)	• Pain	7
2 – Medicines for pain	Adapted from Willebordse et al (2016) medicine review questionnaire	• Current analgesics • Previous analgesics • Reasons for stopping	8
3 – Medical conditions and other medicine	Medicine questions Contraception Medical conditions	• Medicine use • Contraception use • Specific medical conditions • Depression	5
4 – Health and wellbeing	SF-12 (Gandek et al., 1998) PHQ-2 (Löwe et al., 2005)	• Physical limitations • Social limitations • Limitations due to physical health problems • Pain • Mental health • Limitations due to emotional problems • Vitality	12

Section	Measure/tool	Categories	Number of items
		General health perceptions	
5- Sexual health	STEFFI-5 (Kriston et al., 2010)	• Sexual satisfaction • Sexual function • Frequency of sexual intercourse	17
6 – About you	Demographic questions	• Age • Marital status • Living situation • Children • Height/weight • Smoking status • Alcohol • Illegal drug use • Employment • Ethnic origin	13
7 – Consent form	Consent form	Consent to review medical record	1

Table 8-4 Reading age for each section of the self-report questionnaire.

Questionnaire Tool	Flesch-Kincaid grade level	Age
Section 1 PAIN grade*	11.3	16-17
Section 2 Medicines for pain	4.7	9-10
Section 3 Medical conditions and other medicines	4.8	9-10
Section 4 SF-12*	8.8	13-14
Section 5 STEFFI*	5.6	10-11
Section 6 About you	3.1	8-9
Overall	6.4	11-12

Those sections marked with a * are pre-validated measures.

8.7.9 Format of the survey questionnaire

When designing a questionnaire there should be an appropriate flow of questions, so that it is not off-putting to those completing it. The first question must seem relevant to the topic being investigated, and should not be a sensitive question, as this may discourage the participant from completing the rest of the questionnaire (2005). The questionnaire was ordered so that sensitive questions surrounding FSD were not the first questions the participant was asked. Questions on pain and analgesics were placed first to ensure that the questions seemed relevant to the description of the study from the patient information leaflet.

The questionnaire was kept as short as possible whilst asking for information that is necessary for the study. A Cochrane review found a 64% increase in response rate when short questionnaires were used compared to long questionnaires (Edwards et

al., 2009). It is important to note however that there was no definition of what constituted either short or long questionnaires in the review.

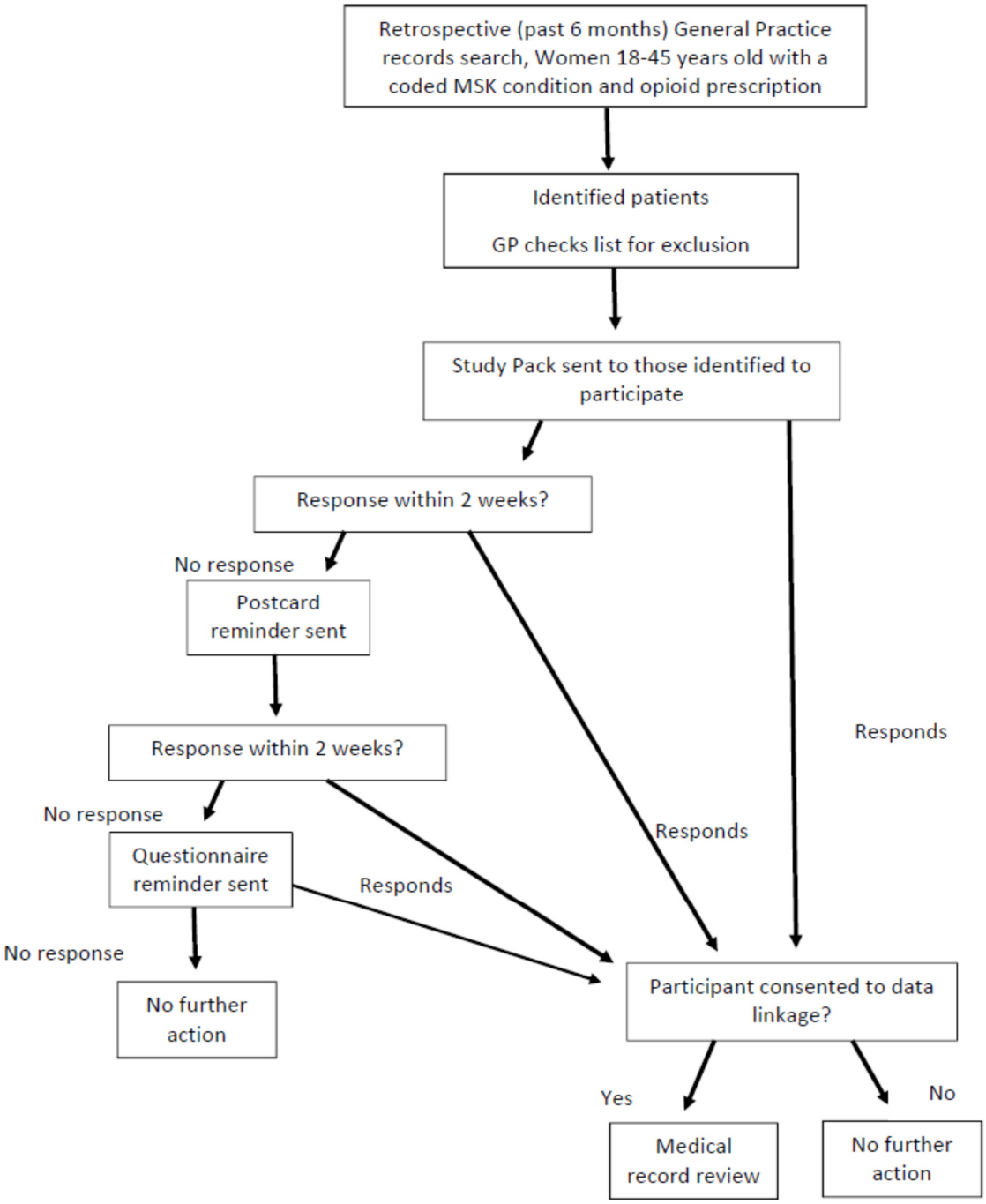
The overall formatting of the questionnaire was led by the SF-12, which is licensed and the formatting of this could not be changed. The remainder of the questionnaire was formatted in the same style, as it was important that the questionnaire remained consistent throughout. Questions were not split over pages in order to minimise the chance of questions being misread and thereby leading to participants reporting answers they did not intend (Bowling, 2014c). Options that are ordinal have been laid out horizontally throughout the questionnaire to also help respondents avoid the misreading of questions and an unintended answer being given.

8.8 Recruitment process

A retrospective medical records search was conducted on a single occasion in each practice, examining the previous six months to identify eligible participants. The search identified women with an opioid prescription (group three to five, moderate to very potent opioids as defined by Bedson et al.2010) and a coded potentially painful musculoskeletal condition within the previous six months (Bedson et al., 2010). The codes used were from the KAPS and STAMP trial as described in section 8.6.3, these were developed to identify painful musculoskeletal conditions, this is not the same code list that was used for the CPRD cohort study (Bedson et al., 2019b; Campbell et al., 2016) A database query produced a list of names and addresses for potentially eligible participants. GPs screened this list against study exclusion criteria and for suitability. Those women identified from the initial search and deemed to be appropriate were mailed the study pack from the practice. Each participant was given

a unique study identifier; this was used to target reminders and for medical record review linkage. The study pack included a covering letter from the GP, a patient information leaflet, the questionnaire itself and a consent form. The questionnaire and consent form were marked with the participant's unique study identifier. The patient information leaflet contained all relevant information relating to the study in order to allow the participant to give informed consent for medical records review. If there was no response, a postcard reminder was sent at two weeks, and a further study pack was sent two weeks later as per research centre standards, see Figure 8-1 (Keele University, 2017). When a further copy of the questionnaire is included with reminder mailings the response rate has been shown to increase 46%, but using a postcard for the initial reminder is a more cost effective approach (Edwards et al., 2009; Roberts et al., 1993). Reminders were coordinated by the research team sending a list of unique study identifiers of those that had already replied with a completed questionnaire to WM:CRN, who then sent out reminders from the practice. Consent for completion of the questionnaire was assumed if a completed questionnaire was returned. Consent for medical records review and future contact was through written consent only (Lacey et al., 2015).

Figure 8-1 Flow diagram of recruitment process for cross-sectional study and data collection



8.9 Baseline assessment

The participant was mailed a study pack that included the questionnaire, which took approximately 20 minutes to complete. An overview of data collection is provided in Table 8-5. The questionnaire included:

- Sociodemographic variables: age, work status, relationship status, ethnicity
- Lifestyle factors: alcohol, smoking, illegal drug use
- Height and weight (for BMI)
- Pain status (chronic pain grade questionnaire)
- Medicine use (including current and recent opioid use, reasons for stopping medicine and current contraception use)
- Sexual function assessed through the use of STEFFI-5 which is described below
- General mental and physical health assessed through the use of SF-12
- Past medical history including important conditions that are associated with FSD (anaemia, hypertension, depression, hysterectomy, diabetes, pelvic pain)

8.10 Medical record review

For patients who consented to medical record review, data was extracted by practice staff regarding prescribed medicines (including pain medicine), recorded sexual dysfunction, age, height, weight, BMI, existing chronic diseases (for instance thyroid disease and pelvic pain). The medical records were anonymised and assigned the unique study identifier that links with the corresponding questionnaire response. Medical records data was used to undertake a sensitivity analysis for logistic regression of opioid dose and FSD, this allowed a larger number of women to be

included in the analysis. Medical records data was not used in preference of self-reported data. The medical records data was also used for a comparison of self-reported FSD with coded FSD within the notes.

Table 8-5: Overview of data collection for cross-sectional study

	Questionnaire	Medical record review
Socio-demographic variables: age, work status, ethnicity	✓	✓
Lifestyle factors: smoking, alcohol, drug use, height, weight	✓	✓
Relationship status	✓	
Contraception	✓	✓
General health (SF-12)	✓	
Opioid use (including previous use and reasons for stopping)	✓	✓
Medicine history	✓	✓
Sexual health: 5 items (STEFFI-5)	✓	✓ (coded diagnosis not based on STEFFI-5)
Pain status (chronic pain grade questionnaire)	✓	
Current medical conditions	✓	✓

8.11 Patient and public involvement and engagement (PPIE)

PPIE is an important part of developing any research study, as it helps to ensure that not only are the research aims relevant and of interest to patients but also that the research methods are considered appropriate by patients and the public. The Research Institute for Primary Care and Health Sciences has an active research user group (RUG) which advises and provides feedback on research projects. The RUG unfortunately does not have any female members between 18 and 45 years old so it was necessary to independently recruit age appropriate women to be involved in a PPIE group for this study.

An initial leaflet was developed by ER to recruit women to participate in the PPIE group. The development was based upon previous leaflets used by the PPIE group. This leaflet was then amended by the Research Institute for Primary Care and Health Sciences PPIE administrative team (Laura Campbell and Adele Higginbottom) to fit with current branding and leaflet style that the PPIE team were using (see Appendix 10). The leaflet was distributed within the Haywood hospital where the local musculoskeletal clinics and IMPACT (chronic pain) clinics are undertaken; unfortunately this did not generate any interest. Consequently, more innovative ways were developed to engage this younger age group who are not traditionally involved in PPIE. Steps were taken to engage women in the appropriate age group through posting on UK pain support websites (painsupport.co.uk and painconcern.org.uk). Those women that responded were included and helped to support the study via either email or an online forum (closed Facebook group). Three women (28-42 years old) responded and they all wished to be included via email only. The women provided feedback on the study pack including the covering letter, tools included in

the questionnaire and the final questionnaire. The women were particularly helpful during the development of the medicine section and completed early drafts, pointing out ways that these could be improved to make them more user friendly. The women reviewed the final version of the questionnaire for face validity (see section 8.7) prior to use within the study.

8.12 Data management

Questionnaire data was entered into a specially designed database, which was tested *a priori* for reliability. The database was developed by ER within Microsoft excel 2013 (Microsoft, 2013b). The database was piloted by an independent reviewer who would be undertaking secondary data input for quality control and suggestions for changes made prior to using the database (Laurna Bullock LB). The changes to the database following review included adding a third column for entering contraception data (so a participant could report three different methods), changing the weight and height section of the database to ensure that these responses could only be entered in one format (either metric or imperial with metric being used preferentially if both were present), If imperial data was entered, this was converted within the database to metric data and used by the database to calculate BMI. Coding of questionnaire responses was determined with input from the study statistician in accordance with the standard procedures within the Research Institute for Primary Care and Health Sciences to facilitate data entry. During data entry the coder only needed to input the answer from the questionnaire and this was then automatically coded by the database. A code book was developed to accompany the database with the possible responses to each question and how to code them explained within this, including when an answer was unable to be coded or there was

a missing response (see Appendix 8). The data was entered from paper questionnaires and there were cross checks (1 in 20) where a second member of the team checked the coding (LB). Checks also took place if there was any data outside the expected range. This ensured reliability and quality assessment throughout the data input process. SF-12 results were calculated through use of software provided as part of the license agreement (Quality Metric Health Outcomes Scoring Software 5.0), data was transferred to the scoring system from the input database (QualityMetric Incorporated, 2016).

8.13 Statistical analysis

The data were entered by ER (with cross checks by LB) into a database developed for the study and was analysed using SPSS 24 by ER (IBM Corp, 2017). The primary comparison was between women currently receiving opioids (with comparison groups of 0mg/day, <20mg/day (low dose opioids) and ≥20mg/day high dose opioids, which have been used as cut off doses in previous research) and previous opioid users (Dunn et al., 2010; Saunders et al., 2009). The demographics of the groups were described using means and standard deviations if normally distributed, and medians and interquartile ranges if non–parametric; categorical items are described using numbers with proportions. The demographics were compared using basic statistical tests. Where data was non-normally distributed a Kruksal-Wallis test was used for significance tests and if the data was continuous ANOVA was used and Fisher's exact test for categorical values. The type (e.g. morphine, codeine) of opioid and duration of opioid use was also compared based on morphine equivalent dose; comparison was undertaken using Chi-squared for duration of opioid use and Fischer's exact test for type of opioid. The numbers of people who stopped different

types of analgesics were presented in a table. The exposure (independent variable) of interest was opioid use and this was split into three groups: previous opioid use, and current opioid use split into <20mg and ≥20mg oral morphine equivalent per day. The outcome (dependent variable) was FSD. The prevalence of women reporting FSD was calculated using proportions and this was compared to the number of women with a diagnosis of FSD on medical records review. Comparison of the proportions of women reporting FSD between current (split by dose) and previous opioids users was undertaken through logistic regression. The effect of opioid use on FSD was expressed as an odds ratios with 95% CIs. Adjustment for potential confounders (SF-12 physical component, SF-12 mental component, age, BMI, PHQ-2, smoking status, alcohol use, NSAID use, contraception and antidepressant use) was done through logistic regression which provided adjusted odds ratios. P values of less than 0.05 (two sided tests) were taken as significant. Due to low response rate it was only possible to undertake univariate analysis and analysis including a second variable rather than multivariable analysis which was initially planned.

Morphine daily equivalent doses were calculated based on the patients reported usage and then converted into morphine equivalents (the corresponding dose of different opioids to morphine) using predefined conversion tables developed by Von Korff et al. for the CONSORT study (Von Korff et al., 2008). MRR data was used for a sensitivity analysis where the dose of prescribed opioids was taken from the notes if the participant did not report a dose, this allowed more women to be split into groups based on daily morphine equivalent dosage.

Survey responders and non-responders were compared using age and level of social deprivation. Social deprivation was calculated based on the postcode of the general

practice each participant was registered with and the index of social deprivation (IMD) which is based on census information and ranks areas within England for 1 (most deprived) to 32,844 (least deprived) (Department for Communities and Local Government, 2015a).

Item non-response was assessed during the data cleaning stage and missing data was dealt with in several different ways. Where data was missing from the self-completion questionnaire, if the participant had agreed to medical records review, appropriate data was taken from this in order to undertake a sensitivity analysis and include further participants. Data was sourced from the medical records for any missing data in relation to comorbidities, medicine names, and doses, MRR data was only used in the case of missing data from the questionnaire in order to undertake a sensitivity analysis. Missing data in SF-12 was dealt with through the software provided with the license for use of the questionnaire. The software employs a method called maximum data recovery to deal with missing data. This is an automatic process where a value is assigned to missing data so long as at least one item in the scale has a response. In order for a PCS and MCS to be calculated certain items must be present within the response (Quality Metric Helth Outcomes, 2016).

A sensitivity analysis was undertaken using STEFFI-2 (instead of STEFFI-5) for the outcome, this increased the number of valid responses and allowed for a larger sample size. A second sensitivity analysis was undertaken using MRR data for opioid dose, this increased the number of women who could be split by total morphine equivalent daily dose and also allowed for a larger sample size to be included.

8.14 Conclusion

This chapter has described the methods of the cross-sectional study including the development of the questionnaire. The following chapter will present the results of the study.

9 Cross-sectional study results

This chapter presents the results of the cross-sectional study undertaken to investigate opioid use and potential associated FSD. The chapter describes the included population first, then compare responders and non-responders, and then by splitting into different opioid user groups. Medicines and comorbidities will be described and compared. FSD will be compared between opioid groups using logistic regression. Finally the results of two sensitivity analyses will be presented.

9.1 Population

Invitations to take part in the study were sent to 1020 women from 29 GPs. The practices included within the study ranged in size from 958 registered patients (with 5 women invited to take part) up to 43838 registered patients (249 women invited to take part). These practices include a wide range of practice types from small single-handed practices to large multi-site practices. See Table 9-1 for information on list size, level of deprivation, number of participants invited per practice and the response rate. As can be seen in Table 9-1 there is a range in proportion (0.12 to 0.92%) of practice list who were invited to participate. All patients who met the inclusion criteria were included in the study, so this represents the difference in prevalence of women with musculoskeletal pain who are prescribed opioids between the different practices. There was also a wide range of index of deprivation (IMD) (described in section 8.7.7 and 8.13) from 1,007 to 30,964 (full range of deprivation in the English population 1 (most deprived)-32,844 (least deprived).

Table 9-1 Characteristics of practices included in the study, with participants invited and response rates

Number of Practices	List size	Index of multiple deprivation	Number of participants invited (%)	Response rate n (%)
29	958	14001	5 (0.52%)	0 (0%)
	2812	1007	26 (0.92%)	7 (27%)
	3974	6975	17 (0.43%)	2 (12%)
	4247	27795	10 (0.24%)	1 (10%)
	4466	20341	10 (0.22%)	2 (20%)
	5164	5840	34 (0.67%)	2 (6%)
	5473	2066	14 (0.26%)	0 (0%)
	5845	25304	17 (0.29%)	5 (29%)
	6292	17311	31 (0.49%)	2 (7%)
	6468	11669	21 (0.32%)	5 (24%)
	6546	28110	9 (0.14%)	3 (33%)
	7121	28579	50 (0.70%)	8 (16%)
	7184	28093	25 (0.35%)	3 (12%)
	7301	22857	9 (0.12%)	3 (33%)
	7427	13694	19 (0.26%)	5 (26%)
	7893	7902	25 (0.32%)	2 (8%)
	7925	21294	15 (0.19%)	2(14%)
	8300	19039	27 (0.33%)	4 (15%)
	8503	30964	21 (0.25%)	2 (10%)
	8980	21792	35 (0.39%)	7 (20%)
	10944	13970	54 (0.49%)	8 (15%)
	11287	22896	52 (0.46%)	13 (25%)
	11852	4759	67 (0.57%)	18 (27%)
	12822	3248	17 (0.13%)	3 (18%)
	13006	15893	44 (0.34%)	8 (18%)
	13202	4423	34 (0.26%)	8 (24%)
	13584	17666	20 (0.15%)	1 (5%)
	16782	1834	63 (0.38%)	3 (5%)
	43838	2444	249 (0.57%)	26 (10%)
Total	270196		1020 (0.38%)	153 (15%)

9.2 Response rate

1020 women were invited to participate in the study. The overall response rate was 15% (153/1020). The response rate ranged from 0% to 33% between practices (see Table 9-1). Six responders were excluded from analysis as they met the exclusion criteria (three were pregnant and three reported being menopausal). All respondents were female. The age range was 18-45 years old. A comparison of responders and non-responders, found responders were statistically significantly older and from practices in less deprived areas, however this was only a small difference with responders being 36 years old and non-responder 35 years old when compared using the mean age (see Table 9-2). The difference in response rate between practices was not statistically significant when compared for practice list size (p=0.84) and index of multiple deprivation (p=0.27). Within responders there was no difference between those who consented for MRR and those who didn't when comparing age and deprivation (see Table 9-3).

Table 9-2 Comparison of age and IMD of responders and non-responders

	Responders	Non-Responders	P
N	153	867	
Age (mean)	36.0	34.6	0.03*
Age (median, IQR)	38 (31-42)	35 (29-41)	
IMD (mean, standard deviation (SD)	12797 (11251-14358)	11208 (10572-11850)	0.02*
IMD (median, IQR)	13694 (3248-22324)	5840 (2444-19039)	

Significance is calculated using Wilcoxon-Mann-Whitney as both Age and Deprivation are non-normally distributed. * indicates significant results.

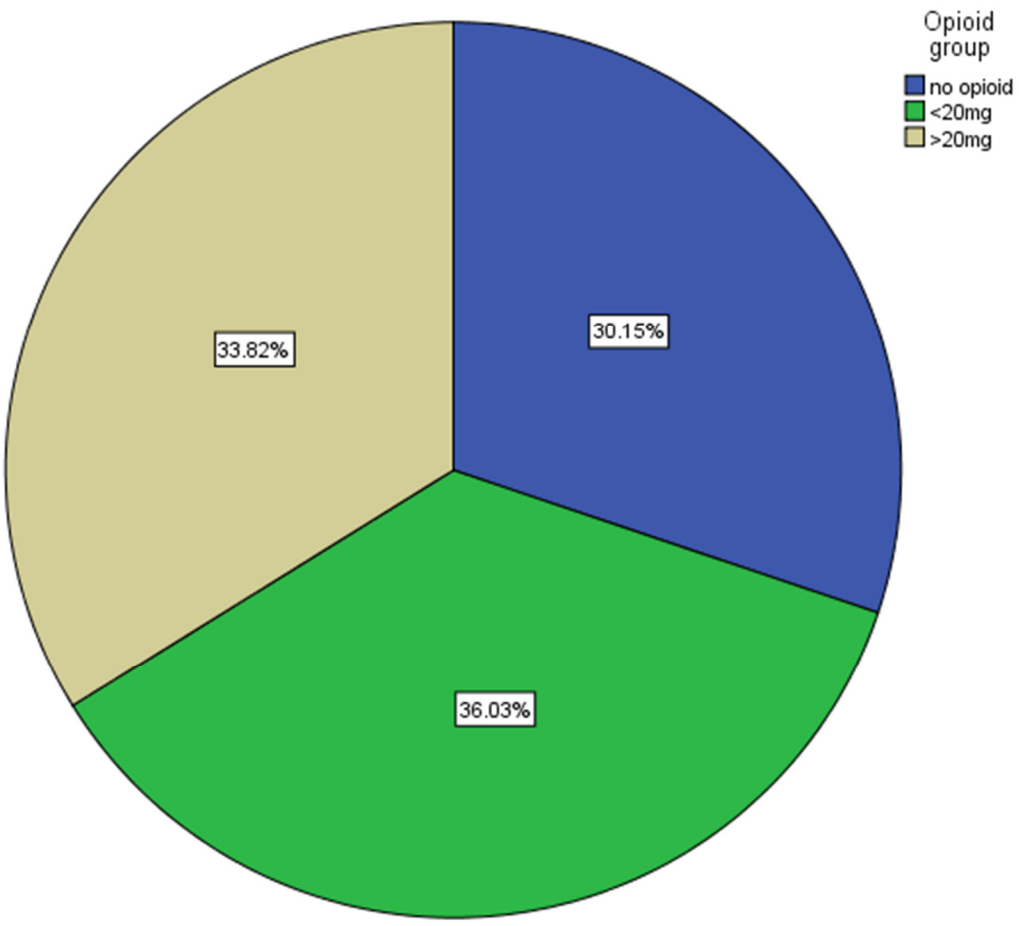
Table 9-3 Comparison of consent status for MRR within responders

	MRR consent	MRR consent withheld	P
N (147)	115	31	
Age (median)	37 (32-42)	37 (31-42)	0.58
Deprivation (median)	11669 (2444-22857)	13694 (4423-20341)	0.82

9.3 Opioid use

146 participants responded and were split into three groups based on opioid dose. 11 (7.5%) current opioid users could not be assigned to a group as there was specific item missing data for the dose of opioids. Of those who could be split into opoid groups 41 (30.2%) participants were not current opioid users (defined in this case as a participant who did not report using opioids at the time of questionnaire), 46 (36.0%) were using a daily morphine equivalent dose of <20mg/day and 48 (33.8%) were using a daily morphine equivalent dose of ≥20mg/day (see Figure 9-1).

Figure 9-1 Pie chart showing the proportion of the sample in each opioid group based on daily morphine equivalent dose



The highest number of different opioids any one person was taking was 4. This participant was an outlier with the next 4 highest participants taking only 2 different opioids. The majority of opioid users reported using only one opioid, with those in the ≥20mg group being more likely to be using 2 different opioids (p<0.001) (see Table 9-4).

Table 9-4 Number of different opioids being used split by opioid group based on daily morphine equivalent dose.

	Whole group	Opioid Category			P
		No Opioid	<20mg/day	≥20mg/day	
N	146	41 (28.1%)	46 (31.5%)	48 (32.9%)	
Number opioids~					
0 opioid	41 (28.1%)	41 (100.0%)	0 (0.0%)	0 (0.0%)	<0.001*
1 opioid	86 (58.9%)		42 (91.3%)	35 (72.9%)	
2 opioids	18 (12.3%)		4 (8.7%)	12 (25.0%)	
3 opioids	0 (0.0%)		0 (0.0%)	0 (0.0%)	
4 opioids	1 (0.7%)		0 (0.0%)	1 (2.1%)	

Where data is non-normally distributed Kruskal-Wallis test has been used for significance tests and medians and IQR have been displayed, indicated with a ~, normally distributed continuous data is compared using ANOVA and fishers exact test for categorical values. Statistical tests do not include comparison to the whole group but are between the three types of opioid use. * indicates statistically significant results

Within those using opioids, the length of use (split into short-term and long-term opioid use) did not vary dependent on the daily dose of opioid used. 91.3% those using ≥20mg/day of morphine were taking opioids long-term (three months of opioid use or longer), compared with 82.2% in the <20mg/day group but this difference was not statistically significant (see Table 9-5). The maximum dose of opioids being used was 900mg/day, the next highest dose was 357mg/day, the third highest dose was 240mg/day with the remaining participants all taking less than 100mg/day of opioids, all three of the women taking the highest doses were in the high disability, severely limiting pain group.

Table 9-5 Length of opioid use and the daily morphine equivalent dose within each group split by opioid dose.

	Opioid Use		P
	<20mg/day	≥20mg/day	[redacted]
Total	45	46	
Opioid use			
Long-term	37 (82.2%)	42 (91.3%)	0.23
Short-term	8 (17.8%)	4 (8.7%)	
Dose			
Range	0.34-19.00	20.00 – 900.00	[redacted]
Median (IQR)	9.0 (2.9-18.0)	38.0 (36.0 – 45.3)	

Comparison using Chi-squared.

The most frequent opioid prescribed was codeine (58.5%, including combination preparations), followed by tramadol (15.4%), dihydrocodeine (13.0%) and then morphine (7.3%). In those taking ≥20mg/day the proportion of codeine fell to 44.1% (compared to 78.8% in the <20mg/day users), and the proportion of those prescribed tramadol, dihydrocodeine and morphine increased. In those receiving <20mg/day of daily morphine equivalent dose no participants reported using morphine whereas 11.9% of those on higher doses reported using morphine. The difference in type of opioid was statistically significant ($p<0.001$) see Table 9-6.

Table 9-6 Types of analgesia prescribed dependent on strength of opioid.

Opioid Type	N (%)	Opioid use		P
		<20mg/day	≥20mg/day	
All	123	52	59	
Morphine	9 (7.3%)	0 (0%)	7 (11.9%)	<0.001*
Codeine	72 (58.5%)	41 (78.8%)	26 (44.1%)	
Tramadol	19 (15.4%)	4 (7.7%)	14 (23.7%)	
Dihydrocodeine	16 (13.0%)	4 (7.7%)	9 (15.3%)	
Oxycodone	3 (2.4%)	1 (1.9%)	2 (3.4%)	
Transdermal Fentanyl	1 (0.8%)	0 (0%)	0 (0%)	
Buprenorphine	3 (2.4%)	2 (3.8%)	1 (1.7%)	

NB total numbers when adding <20mg group to ≥ 20mg will not equal the total numbers in N as some participants were unable to be split within groups as they did not provide doses for medicines. * indicates that the result is statistically significant. Fishers exact test undertaken for comparison.

When comparing type of opioid used based on the duration of opioid use, there was no statistically significant differences (p=0.61), however there were low numbers in the short-term/previous user group (see Table 9-7).

Table 9-7 Types of analgesia prescribed dependent on length of opioid use.

Opioid Type	N (%)	Opioid use		P
		Short-term and previous	Long-term	
All	123	15	99	
Morphine	9 (7.3%)	0 (0%)	8 (8.1%)	0.61
Codeine	72 (58.5%)	8 (53.3%)	60 (60.6%)	
Tramadol	19 (15.4%)	4 (26.7%)	13 (13.1%)	
Dihydrocodeine	16 (13.0%)	3 (20.0%)	11 (11.1%)	
Oxycodone	3 (2.4%)	0 (0.0%)	3 (3.0%)	
Transdermal Fentanyl	1 (0.8%)	0 (0.0%)	1 (1.0%)	
Buprenorphine	3 (2.4%)	0 (0.0%)	3 (3.0%)	

NB total numbers when adding long-term and short-term will not equal the total numbers in N due to missing data.

9.4 Demographics

The demographics for the groups are described below with figures for all responders and then split by opioid use into previous opioid users, current users taking <20mg/day total morphine equivalent dose, and current users taking ≥20mg/day total morphine equivalent dose (see Table 9-8). Doses throughout the chapter represent total morphine equivalent.

146 women responded. The majority of respondents were White (132/146, 90.4%). The median age of responders was 37 (31-42), More than half of respondents were currently in paid employment (84/146, 57.5%) with only 9/146 (6.2%) reporting being off work on sick leave currently. The median IMD was 12682 (IQR 3248 to 21792). The above factors were also compared between different daily total morphine equivalent doses. The proportion of Asian respondents was higher in those who had previously used opioids than in the whole group and current opioid users (see Figure 9-2), however this was not statistically significant (see Table 9-8). Women in the ≥20mg/day category had a higher median age (39.5 years (33-43)), when compared to other opioid groups, this was not statistically significant. There was a statistically significant difference between groups of opioid use with regards to employment ($p<0.001$ see Table 9-8), with the proportion in paid employment decreasing with increasing opioid dose (see Figure 9-3). Level of deprivation was not normally distributed. Level of deprivation showed a trend towards increasing deprivation with increasing daily morphine equivalent dose, this was not statistically significant ($p=0.48$).

Table 9-8 Characteristics of the cross-sectional study, overall and split by opioid category.

	Whole group	Opioid Category			P
		No Opioid	<20mg/day	≥20mg/day	
N	146	41 (28.1%)	46 (31.5%)	48 (32.9%)	
Ethnicity					
White	132 (90.4%)	34 (82.9%)	42 (91.3%)	45 (93.8%)	0.27
Other	14 (9.6%)	7 (17.1%)	4 (8.7%)	3 (6.3%)	
Age (years)~	37 (31, 42)	36 (32, 41)	36.5 (29, 42)	39.5 (33, 43)	0.24
Employment					
Paid job	84 (57.5%)	33 (80.5%)	27 (58.7%)	19 (39.6%)	<0.001 *
Voluntary job	2 (1.4%)	0 (0.0%)	2 (4.3%)	0 (0.0%)	
Employed but off sick	9 (6.2%)	1 (2.4%)	0 (0.0%)	6 (12.5%)	
Looking after home	24 (16.4%)	4 (9.8%)	9 (19.6%)	9 (18.8%)	
Retired	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Student	4 (2.7%)	1 (2.4%)	1 (2.2%)	1 (2.1%)	
Other	23 (15.8%)	2 (4.9%)	7 (15.2%)	22 (16.3%)	
IMD~	12682 (3248, 21792)	13694 (3248, 22896)	11669 (2444, 19039)	5299.5 (2444, 21792)	0.48

Where data is non-normally distributed Kruskal-Wallis test has been used for significance tests and medians and IQR have been displayed, indicated with a ~. Normally distributed continuous data is compared using ANOVA and fishers exact test for categorical values. Tests are for differences between opioid use groups. * indicates statistically significant results.

Figure 9-2 Ethnicity split by group based on daily morphine equivalent dose

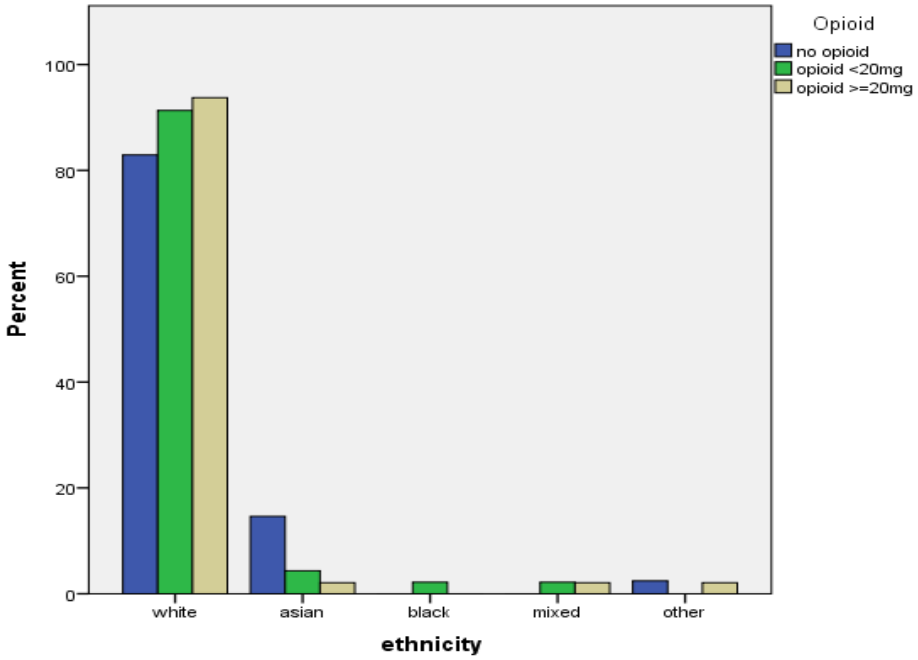
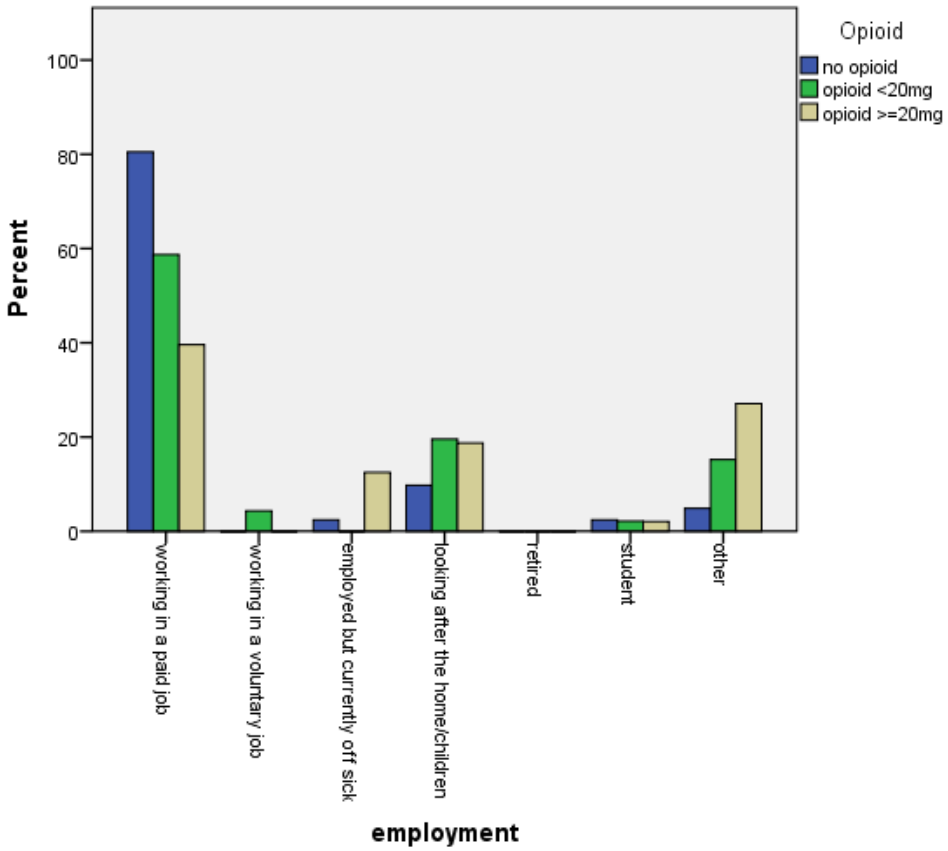


Figure 9-3 Employment status of respondents split by group based on daily morphine equivalent dose



70/146 (48.0%) of the sample overall were married with a further 32/146 (21.9%) co-habiting. There was no statistically significant difference seen with regards to home life between opioid groups including, relationship status (p=0.63), having children (p=0.69) and the number of children (p=0.16) see Table 9-9. Around half of the respondents were married and this was steady across all three groups. Less than 30% of women reported being single see Figure 9-4. 74.0% of the respondents reported having children with a median number of children of 2 (IQR 0, 3) and a range of 0, 5 see Figure 9-5.

Table 9-9 Relationship and child status of the sample overall and split by opioid category

	Whole group	Opioid Category			P
		No Opioid	<20mg/day	≥20mg/day	
N	146	41	46	48	
Relationship status					
Married	70 (48.0%)	19 (46.3%)	21 (45.7%)	26 (54.2%)	0.63
Separated	3 (2.1%)	0 (0.0%)	2 (4.3%)	1 (2.1%)	
Divorced	4 (2.7%)	0 (0.0%)	1 (2.2%)	2 (4.2%)	
Widowed	34 (23.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Co-habiting	32 (21.9%)	13 (31.7%)	9 (19.6%)	10 (20.8%)	
Single	32 (21.9%)	8 (19.5%)	13 (28.3%)	8 (16.7%)	
Missing	2 (2.1%)	1 (2.4%)	0 (0.0%)	1 (2.1%)	
Children					
Yes	108 (74.0%)	31 (75.6%)	32 (69.6%)	37 (77.1%)	0.69
No	38 (26.0%)	10 (24.4%)	14 (30.4%)	11 (22.9%)	
Number of children~	2 (0-3)	2 (1-2)	1 (0 – 2)	2 (0.5 – 3)	0.16

Fishers exact test has been used to compare categorical values, Kruskal-Wallis test for non-normally distributed continuous data indicated by ~ and median and IQR presented.

Figure 9-4 Marital status of respondents split by group based on daily morphine equivalent dose

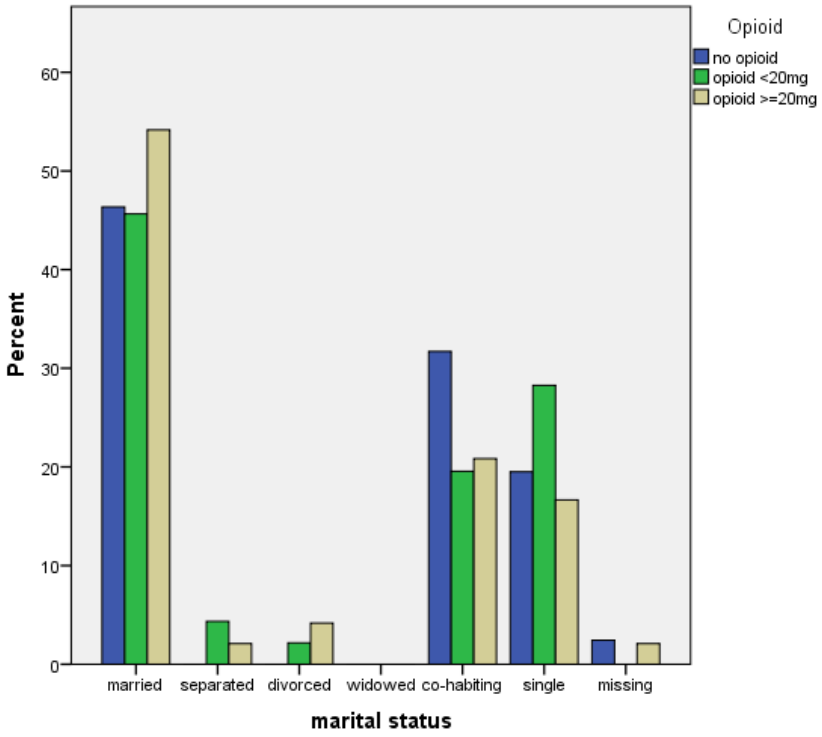
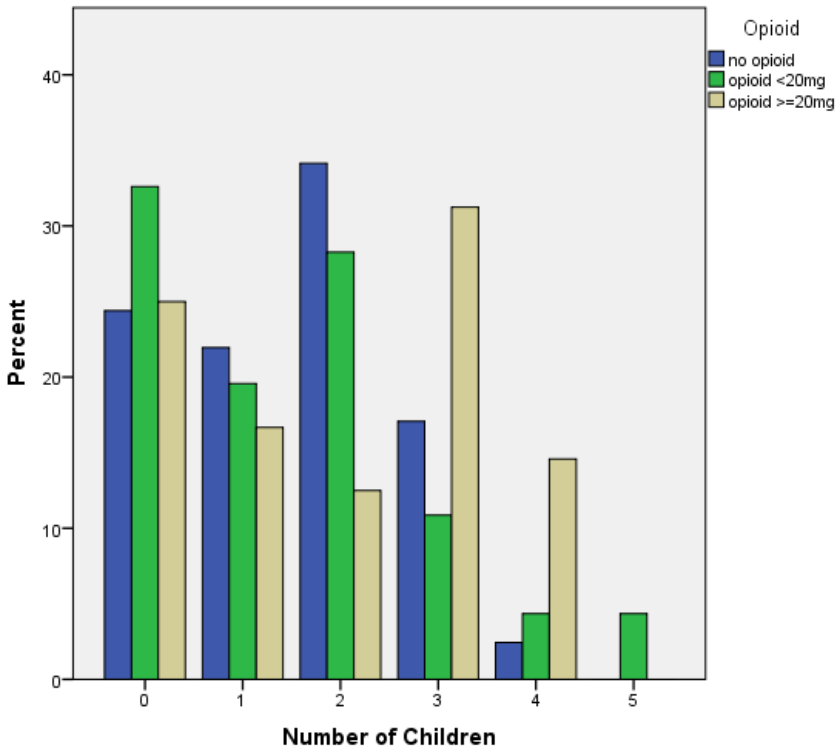


Figure 9-5 Number of children of respondents split by group based on daily morphine equivalent dose



9.5 Smoking, alcohol and illegal drug use

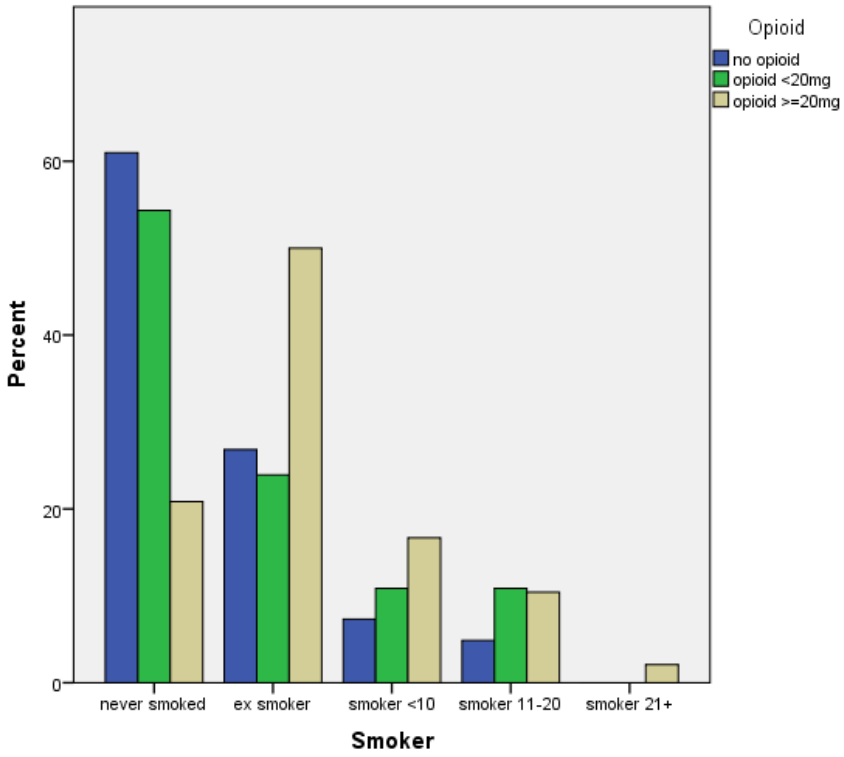
Smoking, alcohol and illegal drug use in the sample are presented in Table 9-10. There appeared to be a trend towards participants being more likely to smoke if they were using opioids, this was not statistically significant (p=0.15) see Figure 9-6. Around one quarter of the participants reported never drinking alcohol (26.0%) and the proportion of non-drinkers seemed to be higher in opioid users but this was not statistically significant (p=0.53) (see Table 9-10). Less than 5% of the respondents reported using illegal drugs and this was seen across all three groups of opioid use (p=1.00).

Table 9-10 Smoking, alcohol and drug use, for the whole group and split by daily morphine equivalent dose.

	Whole group	Opioid Category			P
		No Opioid	<20mg/day	≥20mg/day	
N	146	41	46	48	
Smoking					
Current smoker	34 (23.3%)	5 (12.2%)	10 (21.7%)	14 (29.2%)	0.15
Non smoker	112 (76.7%)	36 (87.8%)	36 (78.3%)	34 (70.8%)	
Alcohol					
Daily	5 (3.4%)	3 (7.3%)	1 (2.2%)	1 (2.1%)	0.53
Once or twice a week	28 (19.2%)	10 (24.4%)	10 (21.7%)	6 (12.5%)	
Once or twice a month	44 (30.1%)	13 (31.7%)	10 (21.7%)	15 (31.3%)	
Once or twice a year	31 (21.2%)	7 (17.1%)	13 (28.3%)	11 (22.9%)	
Never	38 (26.0%)	8 (19.5%)	12 (26.1%)	15 (31.3%)	
Illegal drug use					
Yes	7 (4.8%)	2 (4.9%)	2 (4.3%)	3 (6.3%)	1.00
No	139 (95.2%)	39 (95.1%)	44 (95.7%)	45 (93.8%)	

Fisher's exact test has been used to compare categorical values.

Figure 9-6 Smoking status split by group based on daily morphine equivalent dose



9.6 Physical health

43.8% of the whole group scored 4 (which is the highest grade) on the chronic pain grade, with 28.8% self-reporting chronic pain. The median number of days that participants across the whole group were kept from their usual activities over the preceding 6 months by pain was 23.0 (IQR 7.0, 90.0). The median BMI for the group overall was 28.3 (IQR 23.6, 34.5) and the mean SF-12 physical component score was 42.01 ±11.67 (see Table 9-11).

Higher daily morphine equivalent daily doses were associated with higher pain grade scores, with 62.5% of those in the ≥20mg/day opioid group scoring 4 on the chronic pain grade score compared with only 31.7% in the 0mg group, this was a statistically significant relationship (p=0.01) (see Figure 9-7). Self-reported chronic pain

increased with opioid use (60.4% in the ≥20mg/day opioid group, compared with 4.9% in the 0mg/day group) and this relationship was statistically significant (p=<0.001). Higher opioid dose was associated with participants being kept from daily activities by pain more frequently 69.5 days (IQR 14.75, 160.00) in the ≥20mg/day opioid group compared with 15 days (IQR 2.00, 60.00) in the no current opioid use group and this was also statistically significant (p<0.001) (see Figure 9-8).

Table 9-11 Physical health including pain status, SF-12 physical component and BMI, for the whole group and split by daily morphine equivalent dose.

	Whole Group	Opioid Category			P
		No Opioid	<20mg/day	≥20mg/day	
N	146	41	46	48	
Pain Grade					
1 (low disability low intensity)	14 (9.6%)	6 (14.6%)	7 (15.2%)	1 (2.1%)	0.01
2 (low disability high intensity)	19 (13.01%)	7 (17.1%)	8 (17.4%)	4 (8.3%)	
3 (high disability moderately limiting)	41 (28.1%)	13 (31.7%)	16 (34.8%)	9 (18.8%)	
4 (high disability severely limiting)	64 (43.8%)	13 (31.7%)	14 (30.4%)	30 (62.5%)	
Missing data	8 (5.5%)	2 (4.9%)	1 (2.2%)	4 (8.3%)	
Chronic Pain (self-report)					
Yes	42 (28.8%)	2 (4.9%)	7 (15.2%)	29 (60.4%)	<0.001*
No	98 (67.1%)	33 (80.5%)	39 (84.8%)	19 (39.6%)	
Missing	6 (4.1%)	6 (14.6%)	0 (0.0%)	0 (0.0%)	
Number of days pain has kept them from usual activities in 6 months~	23.0 (7.0, 90.0)	15.0 (2.00, 60.00)	14.00 (4.00, 37.50)	69.50 (14.75, 160.00)	<0.001*
SF-12 physical component	42.01 ±11.67	49.45 ±10.58	43.95 ± 10.48	33.96 ± 8.4	<0.001*
BMI~	28.3 (23.6, 34.5)	24.4 (21.4, 29.6)	28.9 (24.6, 35.4)	32.7 (26.6, 37.3)	<0.001*

Where data is non-normally distributed Kruskal-Wallis test has been used for significance tests and medians and IQR have been displayed, indicated with a ~, normally distributed continuous data is compared using ANOVA and fishers exact test for categorical values.

Figure 9-7 Pain grade split by group based on daily morphine equivalent dose.

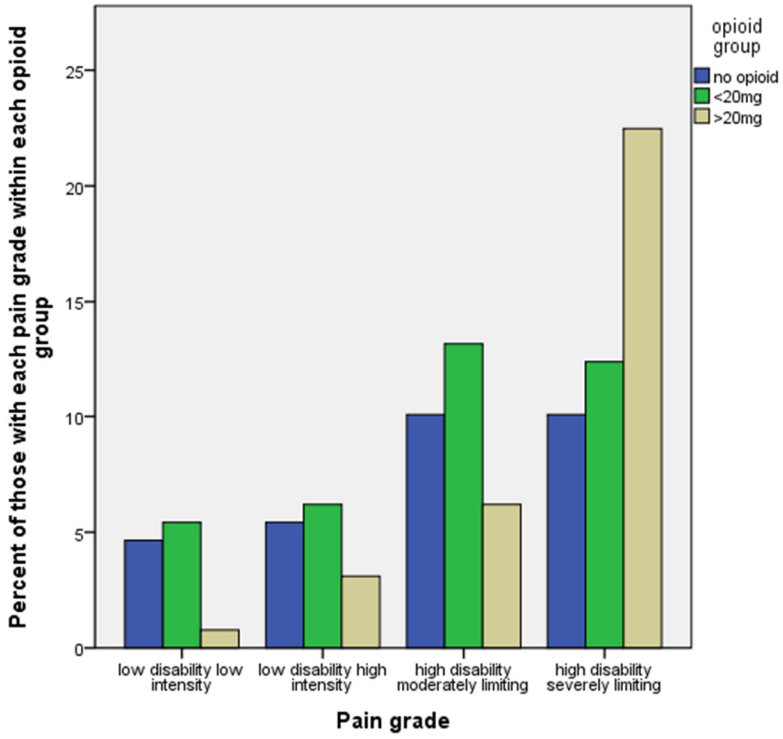
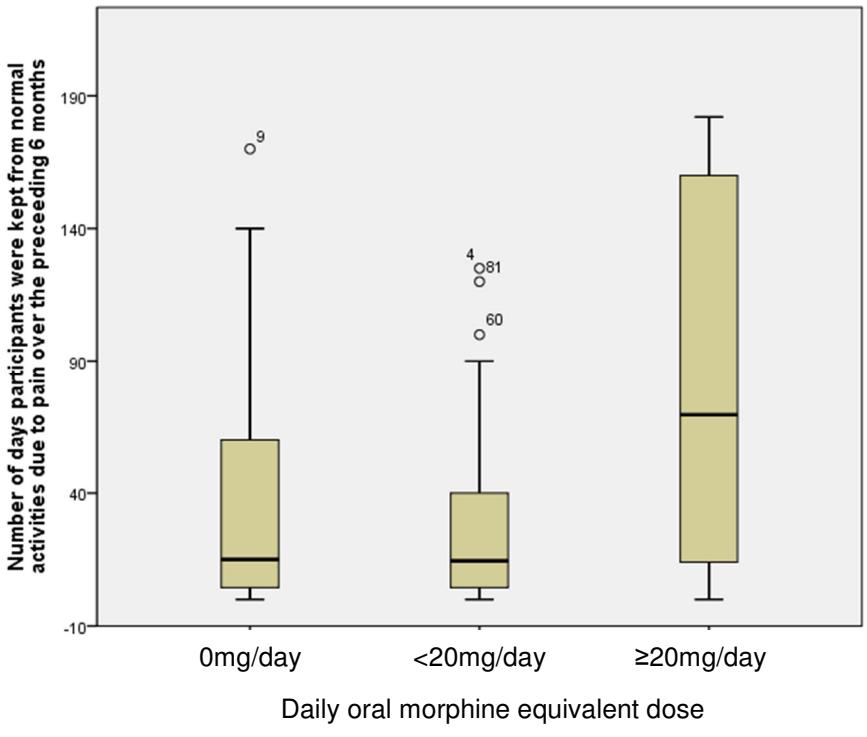
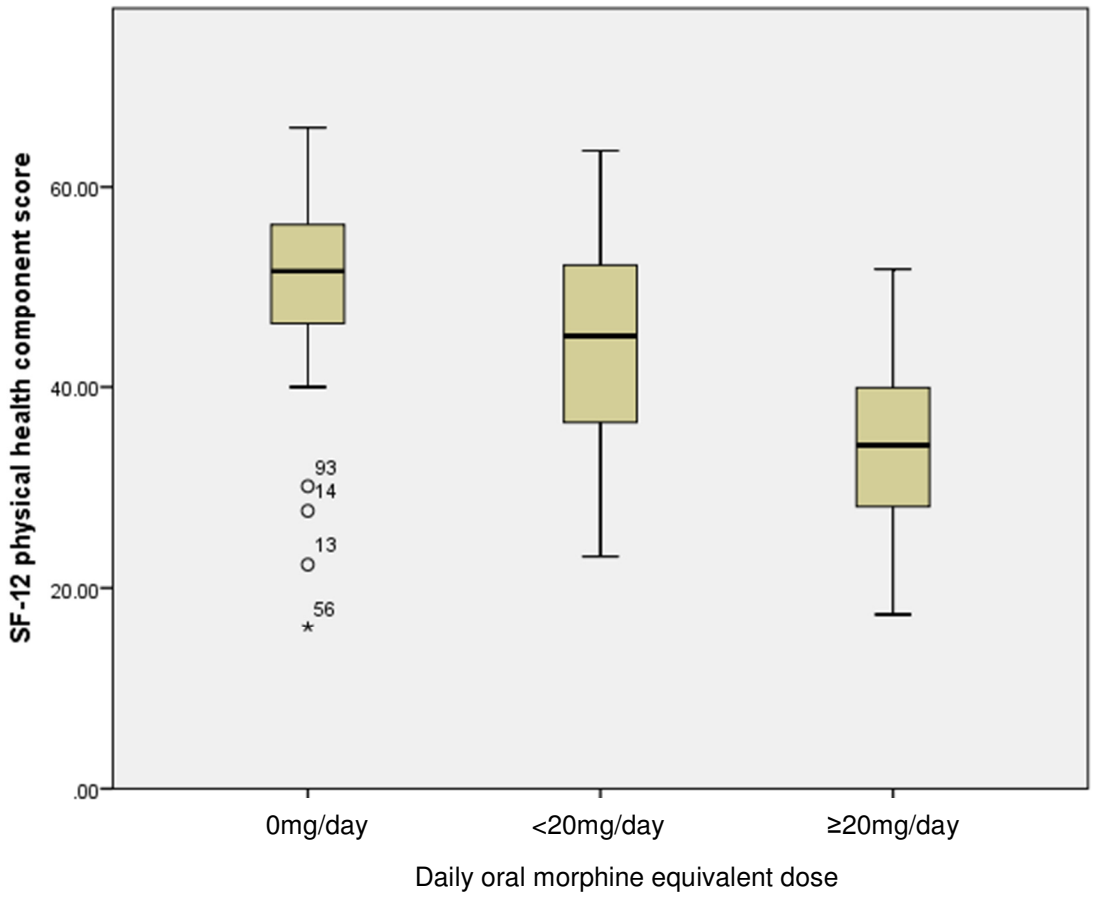


Figure 9-8 Number of days kept from normal activities by pain split by group based on daily morphine equivalent dose.



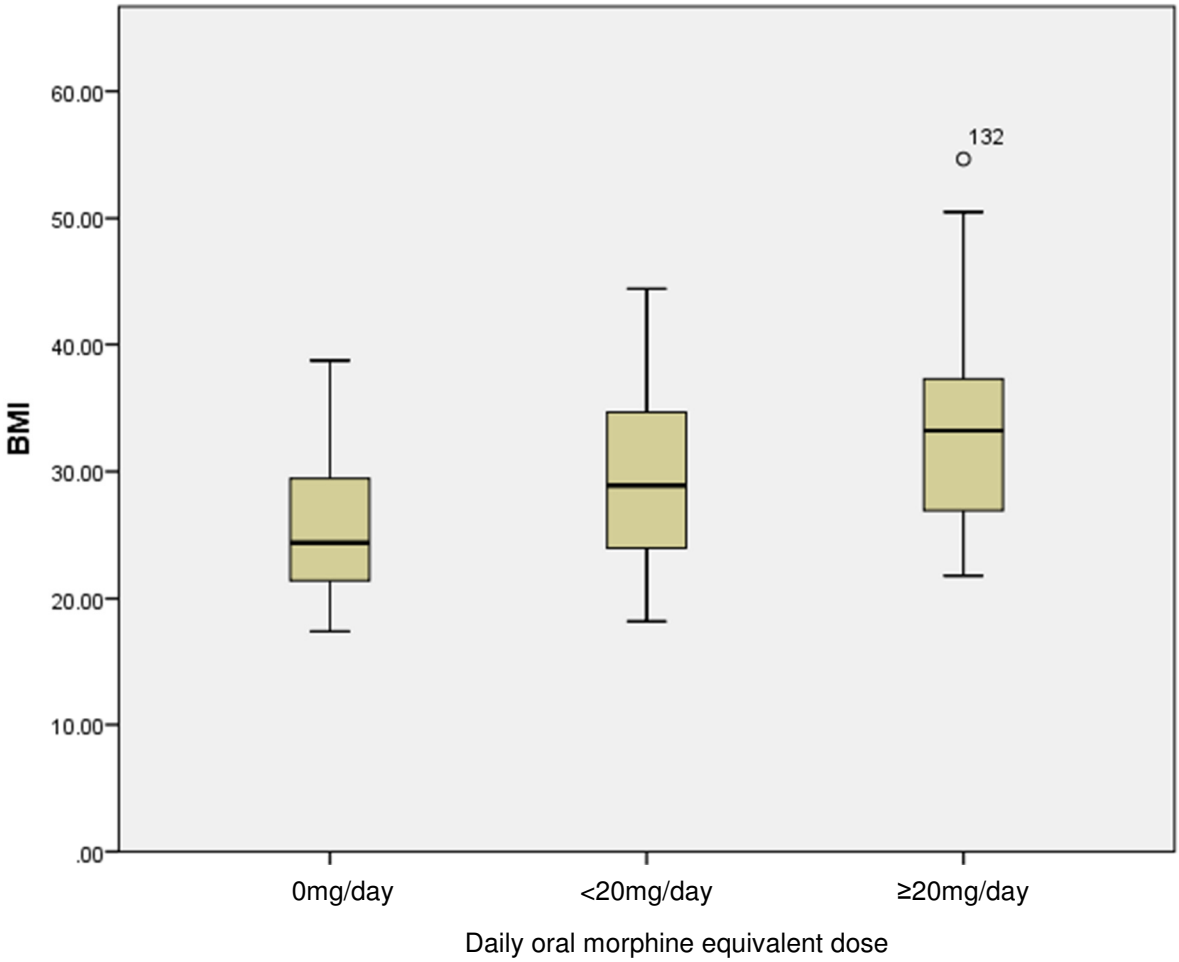
The SF-12 physical component score decreased (the lower the SF-12 physical component score, the worse the participants self-reported physical health) with increasing opioid use, with those in the ≥20mg/day group having the lowest score (33.96 ± 8.4), this was a statistically significant difference between opioid groups ($p<0.001$) see Figure 9-9.

Figure 9-9 SF-12 physical component score split by group based on daily morphine equivalent dose.



Increasing opioid dose was associated with increasing BMI, participants in the ≥20mg/day group had a median BMI of 32.7 (IQR 26.6, 37.3), whereas those in the 0mg/day group had a BMI of 24.4 (IQR 21.4, 29.6) and this was a statistically significant difference (see Figure 9-10).

Figure 9-10 BMI split by group based on daily morphine equivalent dose.



The most common specific physical problem was joint pain, which was reported by 39.7% of the participants. There was a statistically significant difference between opioid groups for joint pain, with the proportion reporting joint pain increasing with daily opioid dose see Table 9-12. No other specific conditions showed a statistically significant difference between groups. Women in the no current opioid group were significantly more likely to report that they had no current medical problems and this decreased with increasing opioid dose.

Table 9-12 Current specific medical conditions described for the whole group and split by group based on daily morphine equivalent dose.

	Whole Group	Opioid Category			P
		No Opioid	<20mg/day	≥20mg/day	
N	146	41	46	48	
Anaemia					
Yes	7 (4.8%)	1 (2.4%)	3 (6.5%)	3 (6.3%)	0.79
No	133 (91.1%)	34 (82.9%)	43 (93.5%)	45 (93.8%)	
Missing	6 (4.1%)	6 (14.6%)	0 (0.0%)	0 (0.0%)	
Hypertension					
Yes	6 (4.1%)	0 (0.0%)	1 (2.2%)	5 (10.4%)	0.07
No	134 (91.8%)	35 (85.4%)	45 (97.8%)	43 (89.6%)	
Missing	6 (4.1%)	6 (14.6%)	0 (0.0%)	0 (0.0%)	
Hysterectomy					
Yes	4 (2.7%)	0 (0.0%)	1 (2.2%)	3 (6.3%)	0.45
No	136 (93.2%)	35 (85.4%)	45 (97.8%)	45 (93.8%)	
Missing	6 (4.1%)	6 (14.6%)	0 (0.0%)	0 (0.0%)	
Thyroid disease					
Yes	11 (7.5%)	1 (2.4%)	3(6.5%)	7 (14.6%)	0.19
No	129 (88.4%)	34 (82.9%)	43 (93.5%)	41 (85.4%)	
Missing	6 (4.1%)	6 (14.6%)	0 (0.0%)	0 (0.0%)	
Joint Pain					
Yes	58 (39.7%)	5 (12.2%)	18 (39.1%)	29 (60.4%)	<0.001*
No	82 (56.2%)	30 (73.2%)	28 (60.9%)	19 (39.6%)	
Missing	6 (4.1%)	6 (14.6%)	0 (0.0%)	0 (0.0%)	
Urinary Incontinence					
Yes	6 (4.1%)	0 (0.0%)	4 (8.7%)	2 (4.2%)	0.20
No	134 (91.8%)	35 (85.4%)	42 (91.3%)	46 (95.8%)	
Missing	6 (4.1%)	6 (14.6%)	0 (0.00%)	0 (0.00%)	
Endometriosis					
Yes	6 (4.1%)	1 (2.4%)	1 (2.2%)	4 (8.3%)	0.45
No	133 (91.1%)	33 (80.5%)	45 (97.8%)	44 (91.7%)	
Missing	7 (4.8%)	7 (17.1%)	0 (0.0%)	0 (0.0%)	
Chronic Pelvic Pain					
Yes	9 (6.2%)	2 (4.9%)	2 (4.3%)	4 (8.3%)	0.90
No	131 (89.7%)	33 (80.5%)	44 (95.7%)	44 (91.7%)	
Missing	6 (4.1%)	6(14.6%)	0 (0.0%)	0 (0.0%)	
No conditions					
Yes	100 (68.5%)	21 (51.2%)	13 (28.3%)	4 (8.3%)	<0.001*
No	40 (27.4%)	14 (34.1%)	33 (71.7%)	44 (91.7%)	
Missing	6 (4.1%)	6 (14.6%)	0 (0.0%)	0 (0.0%)	

Comparison using fishers exact test. * indicates statistically significant results.

9.7 Psychological health

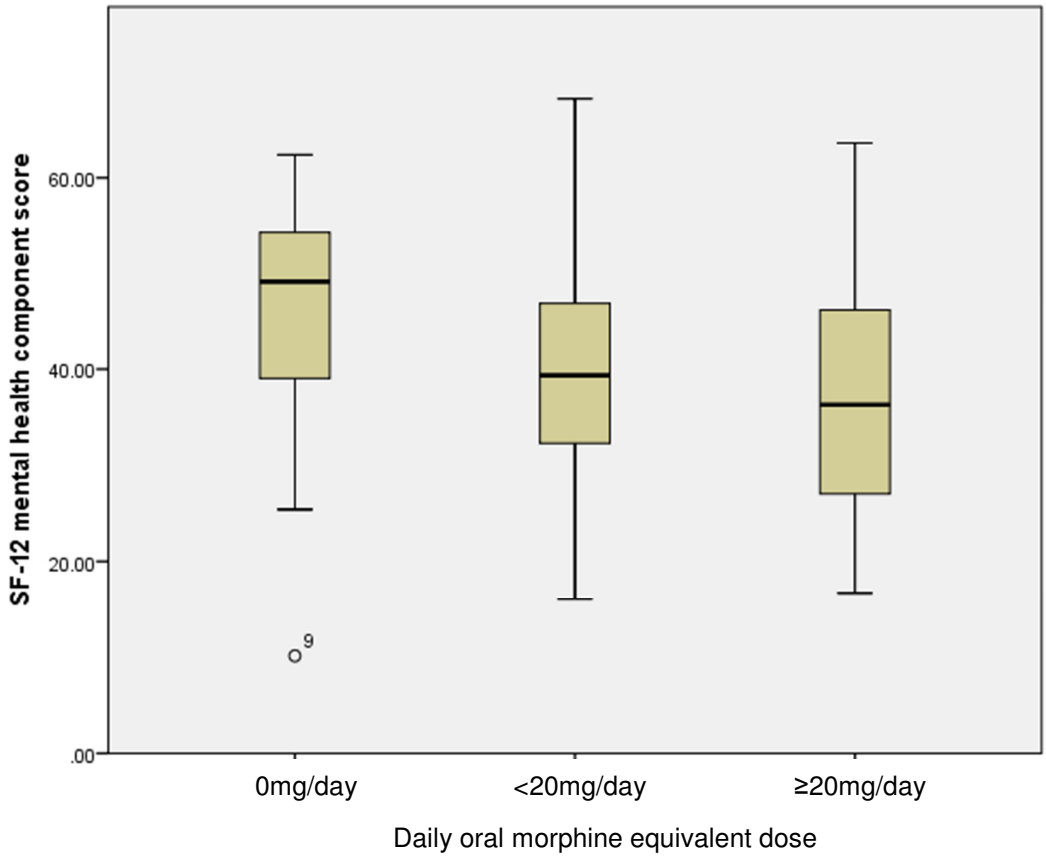
Higher doses of opioids were associated with worsening mental health both self-reported and through use of screening tools (see Table 9-13). There was a statistically significant relationship between opioid use and positive PHQ-2 screening (with a cut off score of 3, p<0.001)), SF-12 mental health component (p<0.001), self-reported depression (p<0.001) and self-reported anxiety (p=0.02). Figure 9-11 shows the SF-12 mental health score for each group of opioid users (lower scores represent poorer mental health), this illustrates the decreasing median for the SF-12 with increasing daily dose of opioid.

Table 9-13 Psychological health described for the whole group and different categories of opioid use based on daily morphine equivalent dose

	Whole group	Opioid Category			P
		No Opioid	<20mg/day	≥20mg/day	
N	146	41	46	48	
PHQ-2 (cut off ≥3)					
Positive	90 (61.6%)	14 (34.1%)	27 (58.7%)	38 (79.2%)	<0.001*
Negative	52 (35.6%)	25 (61.0%)	17 (37.0%)	10 (20.8%)	
Missing	4 (2.7%)	2 (4.9%)	2 (4.3%)	0 (0.0%)	
SF-12 (Mental health component) ~	40.51 (31.9, 48.8)	49.1 (38.3, 54.4)	39.3 (32.2, 49.5)	36.3 (27.5, 45.8)	<0.001*
Patient reported depression					
Present	50 (34.3%)	5 (12.2%)	15 (32.6%)	26 (54.2%)	<0.001*
Absent	90 (61.6%)	30 (73.2%)	31 (67.4%)	22 (45.8%)	
Missing	6 (4.1%)	6 (14.6%)	0 (0.0%)	0 (0.0%)	
Patient reported anxiety					
Present	46 (31.5%)	5 (12.2%)	15 (32.6%)	21 (43.8%)	0.02*
Absent	94 (64.4%)	30 973.2%)	31 (67.4%)	27 (56.3%)	
Missing	6 (4.1%)	6 (14.6%)	0 (0.0%)	0 (0.0%)	

Where data is non-normally distributed Kruskal-Wallis test has been used for significance tests and medians and IQR have been displayed, indicated with a ~, normally distributed continuous data is compared using ANOVA and fishers exact test for categorical values. * indicates a statistically significant relationship.

Figure 9-11 SF-12 mental health score split by group based on daily morphine equivalent dose.



PHQ-2 was used as a marker of mental health disorders within the analysis and this appeared to be reasonable see Table 9-14. A positive PHQ-2 was correlated with self-reported depression and anxiety and worsening SF-12 mental health component score.

Table 9-14 PHQ-2 score compared to pain grade, SF-12 mental component and self-reported anxiety and depression.

	PHQ-2		P
	Negative	Positive	
Pain Grade			
1	8 (15.4%)	5 (5.6%)	0.03*
2	10 (19.2%)	9 (10.0%)	
3	17 (32.7%)	24 (26.7%)	
4	15 (28.8%)	46 (51.1%)	
Missing	2 (3.8%)	6 (6.7%)	
Self-reported depression			
Present	7 (13.5%)	42 (46.7%)	<0.001*
Absent	41 (78.8%)	46 (51.1%)	
Missing	4 (7.7%)	6 (4.2%)	
Self-reported anxiety			
Present	7 (13.5%)	38 (42.2%)	<0.001*
Absent	41 (79.9%)	50 (55.6%)	
Missing	4 (7.7%)	2 (2.2%)	
SF-12 (mental component)	50.4 ± 8.5	34.2 ± 9.4	<0.001*

9.8 Prescribed medicine

9.8.1 Analgesics

Those receiving opioids used a higher number of analgesics overall (see Figure 9-12), were more likely to take paracetamol ($p<0.001$), gabapentoids ($p<0.001$) and antidepressants that can be used for pain ($p<0.001$) (see Table 9-15), these relationships were all statistically significant. There was no statistically significant difference for NSAID use between the three groups of opioid use (see Table 9-15).

Figure 9-12 Number of analgesics taken split by group based on daily morphine equivalent dose

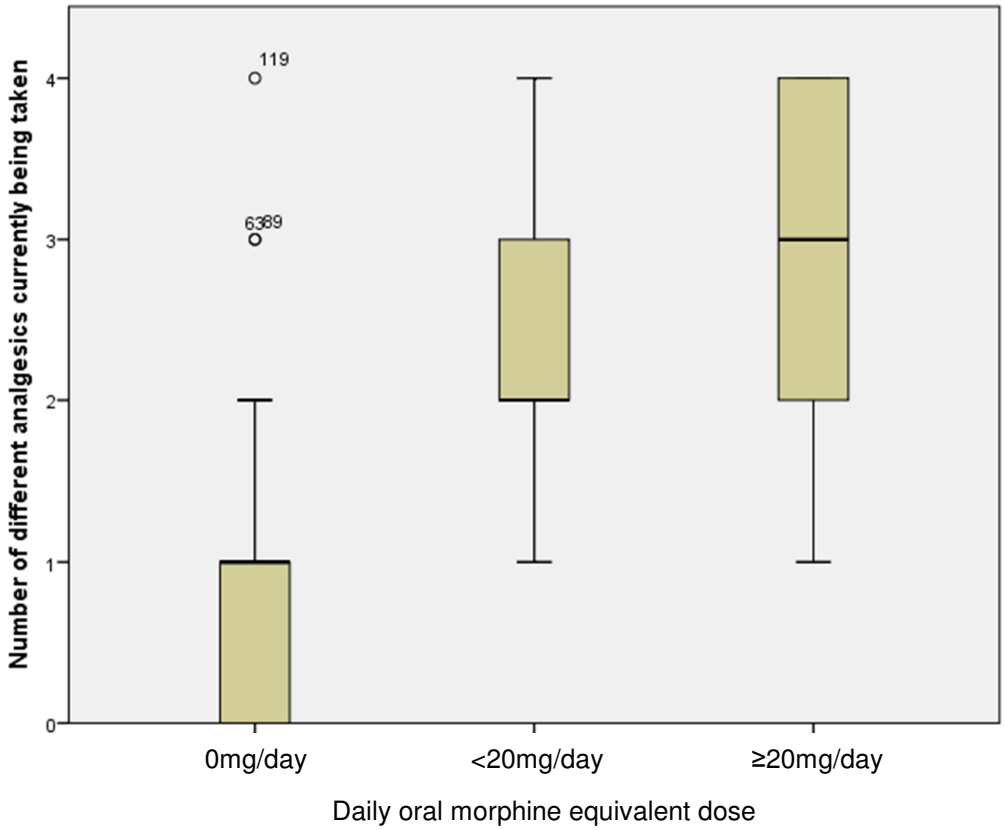


Table 9-15 Analgesic use split by group of opioid use based on daily morphine equivalent dose.

	Whole group	Opioid Category			P
		No Opioid	<20mg/day	≥20mg/day	
N	146	41	46	48	
Number of Analgesics~	2 (1, 3)	1 (0, 1)	2 (2, 3)	3 (2, 4)	<0.001*
Range of analgesics	0, 4	0, 4	1, 4	1, 4	
Paracetamol (alone or in combination form)					
Yes	95 (65.1%)	14 (34.1%)	37 9 (80.4%)	36 (75.0%)	<0.001*
No	51 (34.9%)	27 (65.9%)	9 (19.6%)	12 (25.0%)	
NSAIDs~					
0	77 (52.7%)	25 (61.0%)	23 (50.0%)	26 (54.2%)	0.87
1	63 (43.2%)	14 (34.1%)	21 (45.7%)	20 (41.7%)	
2	6 (4.1%)	2 (4.9%)	2 (4.3%)	2 (4.2%)	
Gabapentoids					
0	127 (87.0%)	41 (100.0%)	40 (87.0%)	37 (77.1%)	<0.001*
1	19 (13.0%)	0 (0.0%)	6 (13.0%)	11 (22.9%)	
Pain Antidepressants					
0	121 (82.9%)	40 (97.6%)	40 (87.0%)	31 (64.6%)	<0.001*
1	25 (17.1%)	1 (2.4%)	6 (13.0%)	17 (35.4%)	

Where data is not normally distributed Kruskal-Wallis test has been used for significance tests and medians and IQR have been displayed, indicated with a ~, normally distributed continuous data is compared using ANOVA and fishers exact test for categorical values. Statistical tests do not include comparison to the whole group but are between the three types of opioid use. * indicates statistically significant results

9.8.2 Reasons for stopping analgesics

When women indicated that they had stopped taking an analgesic medicine they were asked the reasons for this (see Table 9-16). The most common reason for stopping an analgesic was that it didn't help the participant's pain (31.1%). This was highest amongst antidepressant medicines used for pain (50.0%) and NSAIDs (50.0%) and was much lower in those reporting stopping opioids (14.8%). 28.1% of participants who reported stopping medicines said that they did so as they were no longer required. 20.7% of medicines were stopped due to the medicine causing

adverse effects, this was the most common reason for gabapentoids being stopped (54.5% of cases). Focusing on opioids the most common causes for stopping these was that the opioid was no longer needed (35.2%), followed by adverse effects (25.9%) and then by the opioid not helping the participants pain (14.8%).

Table 9-16 Reasons for stopping medicine split by medicine type.

Medicine (n)	Reason for stopping analgesics					
	It didn't help my pain	No longer needed	The medicine made me feel unwell	I was worried about using the medicine	I preferred to try something else	Unable to code
NSAID (40)	20 (50.0%)	9 (22.5%)	6 (15.0%)	4 (10.0%)	0 (0.0%)	1 (2.5%)
Opioid (54)	8 (14.8%)	19 (35.2%)	14 (25.9%)	6 (11.1%)	6 (11.1%)	1 (1.9%)
Paracetamol (10)	4 (40.0%)	4 (40.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
Gabapentoids (11)	3 (27.3%)	1 (9.1%)	6 (54.5%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Benzodiazepines (4)	0 (0.0%)	3 (75.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)
Antidepressants for pain (6)	3 (50.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	2 (33.3%)
Other (9)	4 (44.4%)	1 (11.1%)	1 (11.1%)	1 (11.1%)	2 (22.2%)	0 (0.0%)
Overall (135)	42 (31.1%)	38 (28.1%)	28 (20.7%)	13 (9.6%)	8 (5.9%)	6 (4.4%)

9.8.3 Non-analgesic medicines

The median number of medicines used (including analgesics) was 4 (IQR 2, 6) across the whole group, with those not currently taking opioids using less than this (2, IQR 1, 3) and those in the ≥20mg opioid using more (5, IQR 4, 8.5), This was a statistically significant difference ($p<0.001$) (see Figure 9-13 and Table 9-17) The most medicines any participant was receiving was 16 and the minimum 0. Those receiving opioids were more likely to report taking antidepressants that are traditionally not used as analgesics ($p=0.01$) and were more likely to be receiving an anti-acid medicine (0.00).

Figure 9-13 Number of medicines taken split by group based on daily morphine equivalent dose

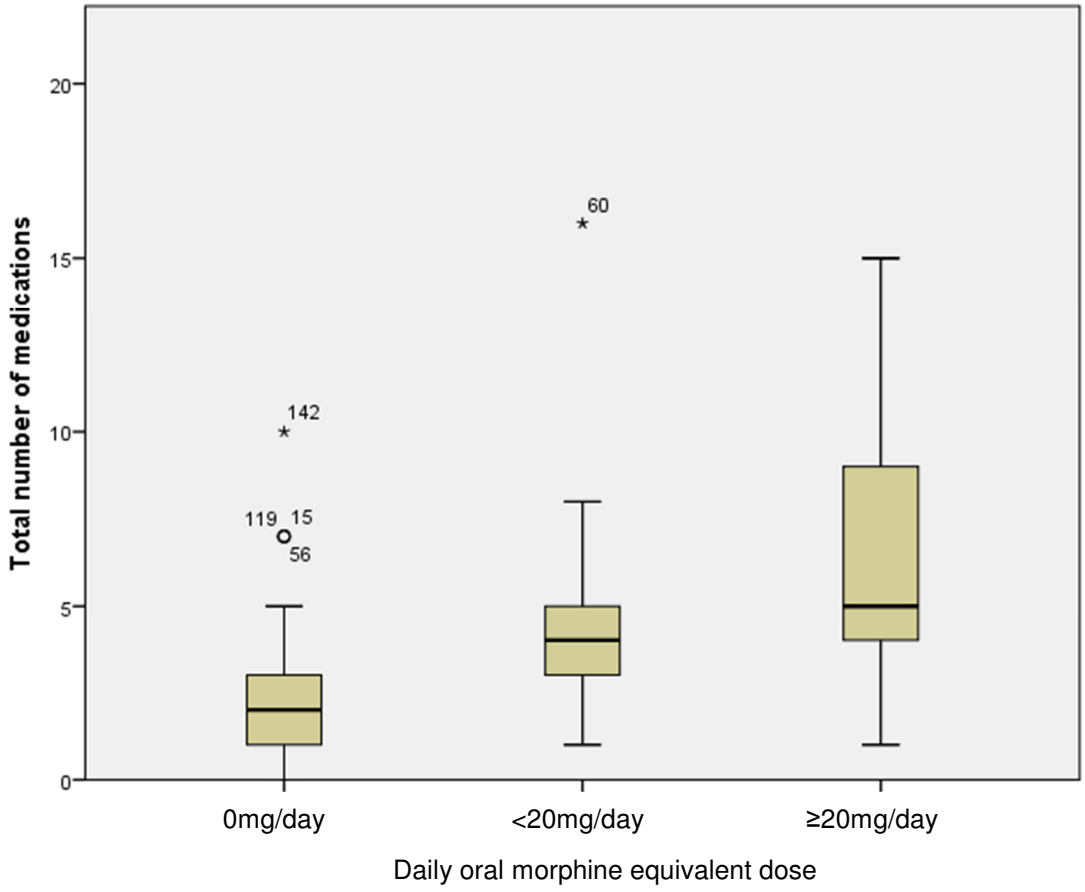


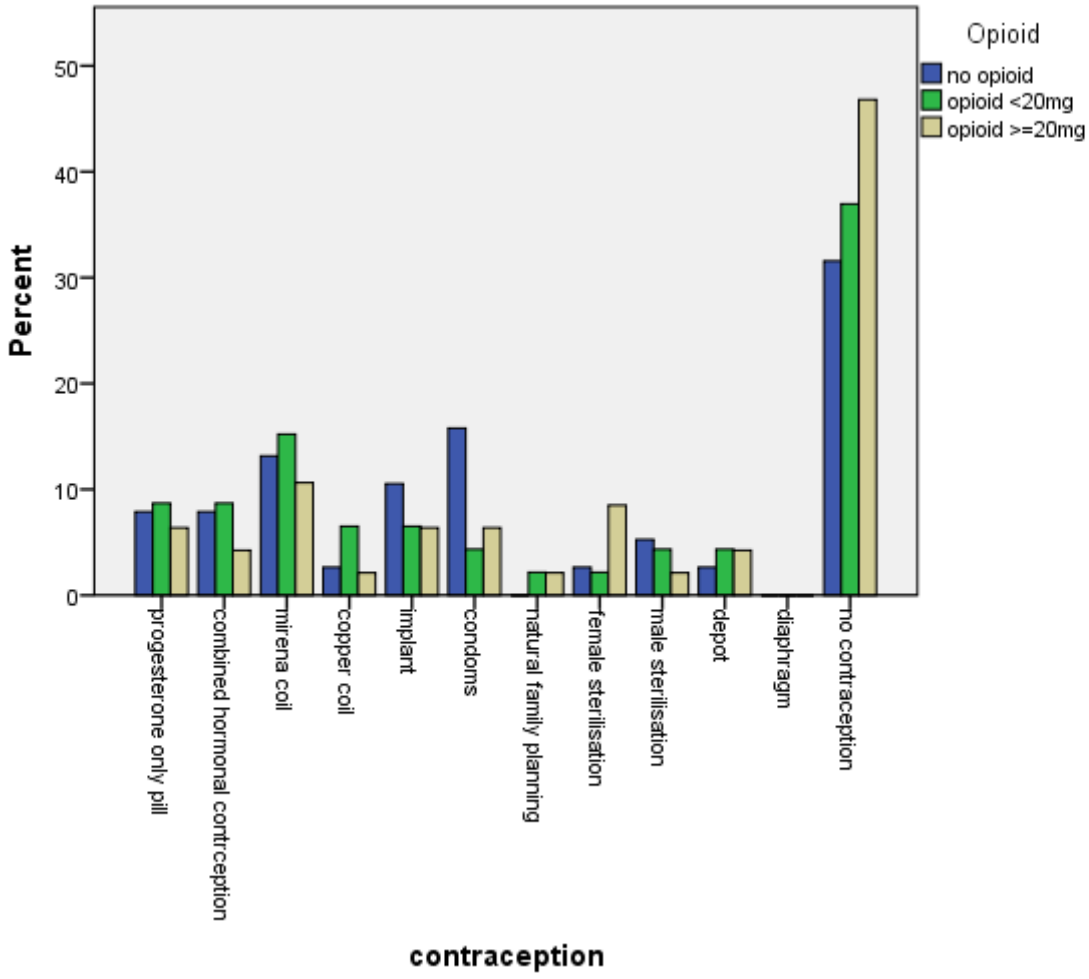
Table 9-17 Non analgesic medicine use for the whole group and split by group based on daily morphine equivalent dose.

	Whole group	Opioid Category			P
		No Opioid	<20mg/day	≥20mg/day	
N	146	41	46	48	
Total number of medicine~	4 (2, 6)	2 (1, 3)	4 (3, 5)	5 (4, 8.5)	<0.001*
Range of medicine	0, 15	0, 10	1, 16	1, 15	
Benzodiazepine/Zopiclone type drugs					
0	136 (93.2%)	40 (97.6%)	41 (89.1%)	46 (95.8%)	0.22
1	10 (6.8%)	1 (2.4%)	5 (10.9%)	2 (4.2%)	
Antidepressants not for pain					
0	111 (76.0%)	38 (92.7%)	34 (73.9%)	32 (66.7%)	0.01*
1	35 (24.0%)	3 (7.3%)	12 (26.1%)	16 (33.3%)	
Contraception					
Hormonal	55 (37.6%)	16 (39.0%)	20 (43.5%)	15 (31.3%)	0.62
Non hormonal	31 (21.2%)	10 (24.4%)	9 (19.6%)	10 (20.8%)	
No contraception	54 (37.0%)	12 (29.3%)	17 (37.0%)	22 (45.8%)	
Missing	6 (4.1%)	3 (7.3%)	0 (0.0%)	1 (2.1%)	
Anti-hypertensives					
0	139 (95.2%)	41 (100.0%)	44 (95.7%)	43(89.6%)	0.12
1	7 (4.8%)	0 (0.0%)	2 (4.3%)	5 (10.4%)	
Anti-acid medicine (Proton pump inhibitors/Histamine 2 blocker)					
0	124 (84.9%)	40 (97.6%)	42 (91.3%)	33 (68.8%)	<0.001*
1	22 (15.1%)	1 (2.4%)	4 (8.7%)	15 (31.3%)	

Where data is non-normally distributed Kruskal-Wallis test has been used for significance tests and medians and IQR have been displayed, indicated with a ~, normally distributed continuous data is compared using ANOVA and fishers exact test for categorical values. Statistical tests do not include comparison to the whole group but are between the three types of opioid use.* indicates statistically significant results.

Just under 60% of the whole cohort reported using contraception of some kind. The proportion of women who report using no contraception appeared to increase with increasing opioid dose but this was not statistically significant (p=0.62) (see Table 9-17). Figure 9-14 shows the specific type of contraception used within each group of opioid use, use of the mirena coil (progesterone intrauterine device) was the second most common category after no contraception use.

Figure 9-14 Contraception use split by group based on daily morphine equivalent dose



9.9 Sexual function

9.9.1 Frequency of sexual intercourse

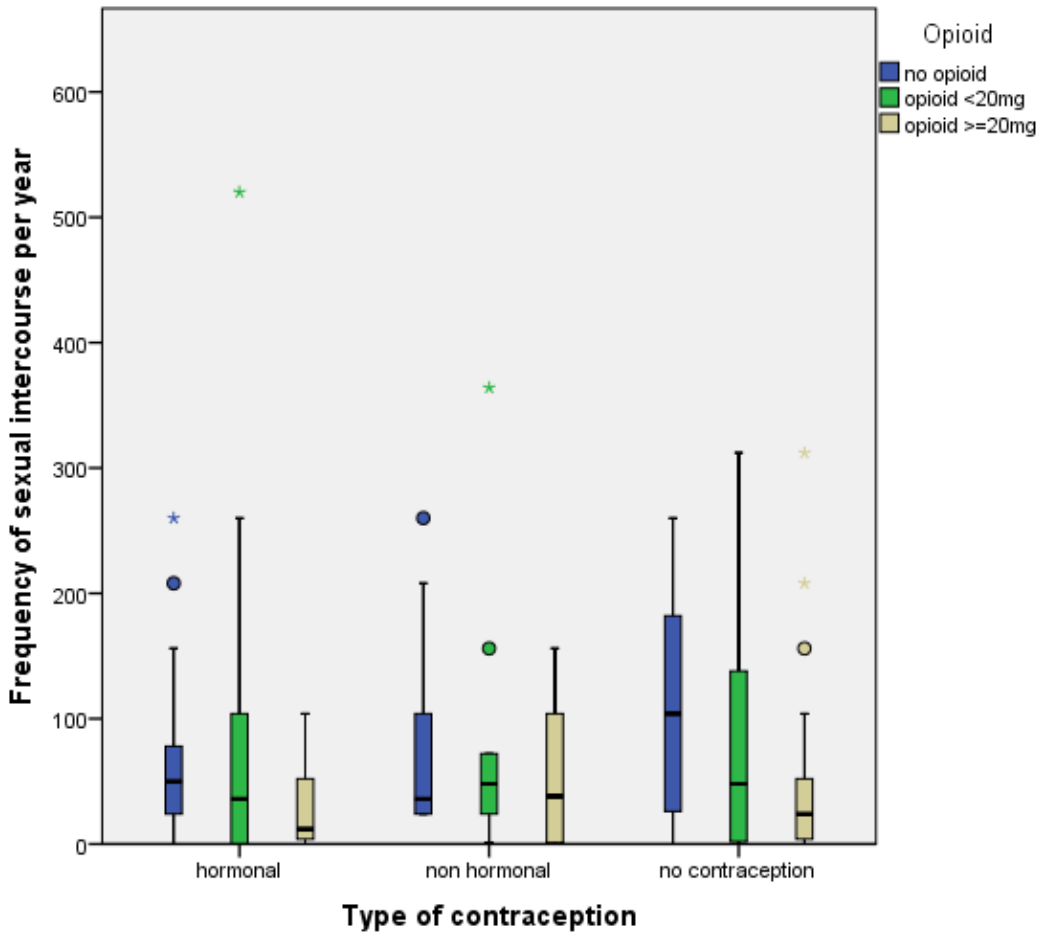
Frequency of reported sexual intercourse ranged from 0-520 per year, with a median of 48 (IQR 5, 104) per year. The participant with the highest frequency was an outlier and the next closest participant reported having sexual intercourse 364 times each year. 25 women reported that they had 0 episodes of sexual intercourse over the course of a year. There appeared to be a decrease in frequency of sexual intercourse with increasing dose of opioid, but this was not statistically significant. There was no relationship between frequency of sexual intercourse, and marital status or type of contraception. The women in the high disability severely limiting group based on pain grade, appeared to have a lower frequency of sexual intercourse, but this again was not statistically significant. The only relationship that appeared to be significant was between FSD (based on STEFFI questionnaire) and frequency of sexual intercourse, with those participants reporting FSD having sexual intercourse less often and this was statistically significant (see Table 9-18 for full details). There is no statistically significant difference between the frequency of sexual intercourse when comparing women receiving different types of contraception dependent on group of opioid use ($p = 0.98$). The data shows that some women are taking opioids and having sexual intercourse without using any form of contraception (see Figure 9-15).

Table 9-18 Frequency of sexual intercourse (number/year) dependent on pain, opioid use, FSD and relationship status.

	N	Sexual intercourse (median, IQR)	P
Whole group	138	48 (5 – 104)	
Opioid use			
No opioid	40	52 (24 – 124)	0.22
Opioid < 20mg/day	42	42 (4 – 120)	
Opioid ≥ 20mg/day	45	24 (4 – 52)	
Marital status			
Married	68	36 (12 – 100)	0.12
separated	3	1 (0-60)	
Divorced	4	24 (12.5 – 38)	
Co-habiting	33	52 (24 – 156)	
Single	28	24 (0-150)	
FSD			
Present	57	24 (0-52)	<0.001*
Absent	74	52 (36-156)	
Pain grade			
1 (low disability low intensity)	14	52 (34-60)	0.14
2 (low disability high intensity)	17	52 (24 – 120)	
3 (high disability moderately limiting)	41	52 (24-104)	
4 (high disability severely limiting)	58	24 (4-52)	
Contraception			
Hormonal	50	48 (5 – 104)	0.66
Non-hormonal	30	50 (24 – 104)	
No contraception	52	42 (4 – 112)	

Tests of significance are Kruskal-Wallis as frequency of sexual intercourse is a non-normally distributed outcome. * indicates significant results

Figure 9-15 Frequency of sexual intercourse split by type of contraception and group based on daily morphine equivalent dose



9.9.2 FSD and medical records review

116 women consented to medical records review. Of these women. 50 of these women had a positive result for FSD based on their response to the STEFFI-5 questionnaire and 8 women did not give enough data for a result for STEFFI-5 to be calculated. None of the women who consented to medical records review had coded sexual dysfunction in the medical notes.

9.9.3 Opioid use and female sexual dysfunction (FSD)

FSD was present in increasing numbers as opioid use increases. 31.7% of those not using opioids report FSD, rising to 50.0% in those using ≥20mg morphine equivalent per day. The difference was not statistically significant but there is increased odds of FSD with those taking increasing doses of opioids. The <20mg group had an OR of 1.28 (0.51, 3.20) and in the ≥20mg 2.29 (0.94, 5.55), which is more than double the odds of FSD than those not currently taking opioids see Table 9-19. A test for trend was not statistically significant (p = 0.09). The logistic regression was restricted to univariate analysis (including just a single covariate or confounder) due to small numbers within the study. The logistic regression was adjusted for clinically important variables individually, to see if they confounded the observed relationship see Table 9-20. There was a consistent relationship across all the outcomes for FSD with increasing daily morphine equivalent dose of opioids associated with increasing odds of FSD, and this pattern remains after adjustment. However none of the OR were statistically significant and the 95% CI were wide.

Table 9-19 FSD including both the overall results of STEFFI-5 and the

	Opioid Category		
	No Opioid	<20mg/day	≥20mg/day
N	41	46	48
FSD			
Present	13 (31.7%)	16 (35.8%)	24 (50.0%)
Absent	26 (63.4%)	25 (54.3%)	21 (43.8%)
Missing	2 (4.9%)	5 (10.9%)	3 (6.3%)
OR (95% CI)	Reference	1.28 (0.51, 3.20)	2.29 (0.94, 5.55)
P	Category	0.60	0.07
Satisfied with sex life			
Yes	25 (61.0%)	24 (52.2%)	25 (52.1%)
No	15 (36.6%)	19 (41.3%)	23 (47.9%)
Missing	1 (2.4%)	3 (6.5%)	0 (0.0%)
OR (95% CI)	Reference	1.32 (0.55, 3.18)	1.53 (0.65, 3.60)
P	Category	0.54	0.33
Partner satisfied with sex life			
Yes	13 (31.7%)	22 (47.8%)	22 (45.8%)
No	27 (65.9%)	19 (41.3%)	26 (54.2%)
Missing	1 (2.4%)	5 (10.9%)	0 (0.0%)
OR (95% CI)	Reference	0.416 (0.17, 1.03)	0.57 (0.24, 1.36)
P	Category	0.06	0.57
Difficulty Orgasming			
Yes	12 (29.3%)	16 (34.8%)	22 (46.8%)
No	28 (68.3%)	26 (56.5%)	24 (51.1%)
Missing	1 (2.4%)	4 (8.7%)	1 (2.1%)
OR (95% CI)	Reference	1.44 (0.57, 3.60)	2.14 (0.88, 5.21)
P	Category	0.44	0.09
Pain during sexual intercourse			
Yes	18 (43.9%)	25 (54.3%)	31 (64.6%)
No	22 (53.7%)	18 (39.1%)	17 (35.4%)
Missing	1 (2.4%)	3 (6.5%)	0 (0.0%)
OR (95% CI)	Reference	1.70 (0.71, 4.05)	2.23 (0.94, 5.26)
P	Category	0.23	0.07
Satisfied with level of sexual desire			
Yes	23 (56.1%)	24 (52.2%)	22 (45.8%)
No	17 (41.5%)	19 (41.3%)	26 (54.2%)
Missing	1 (2.4%)	3 (6.5%)	0 (0.0%)
OR (95% CI)	Reference	1.07 (0.45, 2.55)	1.60 (0.69, 3.73)
P	Category	0.88	0.28
Reports problems with sex life			
Yes	12 (29.3%)	16 (34.8%)	19(39.6%)
No	27 (65.9%)	26 (56.5%)	28 (58.3%)
Missing	2 (4.9%)	4 (8.7%)	1 (2.1%)
OR (95% CI)	Reference	1.39 (0.55, 3.48)	1.53 (0.62, 3.74)
P	Category	0.49	0.35

individual components split by daily morphine equivalent dose.

Table 9-20 Odds Ratio for FSD with adjustment for a single covariate or confounder comparing groups based on daily morphine equivalent dose

OR adjusted for	Adjusted OR (95% CI)	P
Pain grade		
<20mg/day	1.30 (0.52, 3.28)	0.58
≥20mg/day	2.22 (0.88, 5.59)	0.09
SF-12 physical component		
<20mg/day	1.27 (0.50, 3.21)	0.62
≥20mg/day	2.24 (0.77, 6.34)	0.14
SF-12 mental component		
<20mg/day	1.03 (0.39, 2.69)	0.95
≥20mg/day	1.77 (0.69, 4.52)	0.23
Age		
<20mg/day	1.28 (0.51, 3.19)	0.60
≥20mg/day	2.30 (0.94, 5.62)	0.07
BMI		
<20mg/day	1.29 (0.50, 3.37)	0.60
≥20mg/day	2.28 (0.83, 6.24)	0.11
PHQ-2		
<20mg/day	1.21 (0.47, 3.08)	0.69
≥20mg/day	2.01 (0.78, 5.18)	0.15
Smoker (2 categories smoker vs non-smoker)		
<20mg/day	1.28 (0.51, 3.21)	0.59
≥20mg/day	2.30 (0.94, 5.63)	0.07
Alcohol		
<20mg/day	1.20 (0.48, 3.05)	0.70
≥20mg/day	2.12 (0.86, 5.26)	0.10
NSAID		
<20mg/day	1.22 (0.48, 3.07)	0.68
≥20mg/day	2.23 (0.91, 5.43)	0.08
Contraception (2 categories hormonal vs non-hormonal/no contraception)		
<20mg/day	1.15 (0.45, 2.92)	0.77
≥20mg/day	1.97 (0.79, 4.94)	0.15
Antidepressants		
<20mg/day	1.21 (0.48, 3.07)	0.69
≥20mg/day	1.99 (0.75, 3.05)	0.17

No opioid use (0mg/day morphine equivalent dose) is used as the reference group and each analysis is adjusted for the factor shown in the left hand column.

9.10 Sensitivity analysis

9.10.1 FSD measure

The first sensitivity analysis was undertaken by using STEFFI-2 rather than STEFFI-5 to define FSD. This increased the sample size by four women. Undertaking this sensitivity analysis returned a statistically significant odds ratio for those taking ≥20mg/day of oral morphine equivalent dose when compared to those receiving no current opioids (OR 2.39, 95% CI 1.01, 5.67) see Table 9-21 for full details. This relationship became non-significant when adjusted except when adjusted for age and PHQ-2. The largest changes with adjustment were for SF-12 mental component and antidepressants (for any reason).

Table 9-21 Sensitivity analysis using STEFFI-2 as the measure for FSD comparing groups based on daily morphine equivalent dose

	Opioid Category		
	No Opioid	<20mg/day	≥20mg/day
N	41	46	48
FSD			
Present	17 (41.5%)	21 (45.7%)	30 (62.5%)
Absent	23 (56.1%)	21 (45.7%)	17 (35.4%)
Missing	1 (2.4%)	4 (8.7%)	1 (2.1%)
OR (95% CI)		1.35 (0.57, 3.23)	2.39 (1.01, 5.67)
Adjusted OR			
Pain Grade		1.38 (0.57, 3.30)	2.30 (0.95, 5.53)
SF-12 physical		1.32 (0.54, 3.22)	2.22 (0.80, 6.19)
SF-12 mental		0.96 (0.37, 2.44)	1.59 (0.63, 4.02)
Age		1.35 (0.57, 3.24)	2.38 (1.00, 5.67)
BMI		1.55 (0.62, 3.89)	2.65 (0.98, 7.17)
PHQ-2		1.33 (0.56, 3.20)	2.38 (1.00, 5.66)
Smoker (2 categories)		1.35 (0.56, 3.24)	2.38 (0.99, 5.71)
Alcohol		1.31 (0.54, 3.16)	2.28 (0.95, 5.51)
NSAIDs		1.29 (0.54, 3.12)	2.31 (0.97, 5.52)
Contraception (2 categories)		1.30 (0.53, 3.19)	2.35 (0.96, 5.78)
Antidepressants		1.22 (0.50, 2.97)	1.87 (0.73, 4.83)

9.10.2 Opioid dose including medical records review data

The second sensitivity analysis was undertaken by including daily morphine equivalent dose calculated with medical records review data replacing missing data from the questionnaire. This increased the number of participants that could be split by opioid group from 135 to 144. Logistic regression for the sensitivity analysis returned an odds ratio of 2.57 (95% CI 1.07, 6.18) for FSD in those who used ≥20mg morphine equivalent daily compared with no opioid use. Pain during intercourse was also more likely in the highest dose opioid group (p=0.04). Univariate analysis was undertaken for FSD and opioid use, the odds ratio remained significant when adjusted for pain grade, age, BMI and NSAID use. Adjustment for SF-12 physical component, SF-12 mental component, PHQ-2, smoking status, alcohol, contraception and antidepressant use (all indications) decreased the odds ratio and caused the relationship to become non-significant (see Table 9-22).

Table 9-22 Sensitivity analysis using medical records review data comparing groups based on daily morphine equivalent dose

	Opioid Category		
	No Opioid	<20mg/day	≥20mg/day
N	41	51	52
FSD			
Present	13 (31.7%)	16 (31.4%)	27 (51.9%)
Absent	26 (63.4%)	30 (58.8%)	21 (40.4%)
Missing	2 (4.9%)	5 (9.8%)	4 (7.7%)
OR (95% CI)		1.07 (0.43, 2.63)	2.57(1.07, 6.18)
Adjusted OR			
Pain Grade		1.06 (0.43, 2.61)	2.63 (1.05, 6.57)
SF-12 physical		1.05 (0.42, 2.64)	2.44 (0.87, 6.84)
SF-12 mental		0.90 (0.35, 2.30)	2.07 (0.81, 5.24)
Age		1.07 (0.44, 2.64)	2.55 (1.06, 6.15)
BMI		1.14 (0.45, 2.91)	2.76 (1.05, 7.26)
PHQ-2		1.14 (0.44, 2.94)	2.50 (0.96, 6.50)
Smoker (2 categories)		1.10 (0.44, 2.71)	2.66 (1.10, 6.44)
Alcohol		1.01 (0.40, 2.51)	2.38 (0.97, 5.83)
NSAIDs		1.02 (0.41, 2.54)	2.54 (1.05, 6.12)
Contraception (2 categories)		0.95 (0.38, 2.38)	2.18 (0.88, 5.42)
Antidepressants		1.01 (0.41, 2.54)	2.27 (0.87, 5.94)

9.11 Conclusion

This chapter has presented the results of the cross-sectional study undertaken for this thesis which investigates the relationship between opioids and FSD. The results will be summarised in the next chapter and the strengths and limitations of the study will be discussed.

10 Cross-sectional study discussion

This chapter summarises the main findings from the cross-sectional study, and then puts these results in the context of the current literature. The strengths and limitations of the study will be discussed and what the results mean in terms of the population of interest. Finally the unanswered questions from this study and the conclusions that can be drawn from the results will be presented.

10.1 Summary of main findings

The study response rate was 15%; responders were older and more often from less deprived areas when compared with non-responders.

Opioid users were split into three groups, those taking a morphine equivalent dose of ≥20mg/day, those taking a daily dose of <20mg/day and those not currently taking opioids. The majority (79/91, 87%) of those taking opioids were long-term users (three months or longer), with no difference in length of use dependent on opioid dose. The opioid most commonly taken was codeine (58.5% either alone or in combination) followed by tramadol (15.4%), dihydrocodeine (13.0%) and morphine (7.3%). The order of type of opioid use was the same across the groups split by opioid dose, however stronger opioids accounted for a higher proportion of overall use in the ≥20mg/day opioid group. Current opioid use was associated with increased use of other analgesics (paracetamol either in combination or alone, gabapentoids and antidepressants) and total number of medicines used. There was no significant difference in the type of contraception used based on opioid use.

The three groups of opioid use, had statistically significant differences for employment (higher opioid doses were associated with decreased numbers in

employment), physical health (higher opioid doses associated with increased pain grade, increased self-reported chronic pain, increased number of days pain kept them from normal activities, decreased SF-12 physical component, increased BMI, increased joint pain and increased participants self-reported health conditions). Increasing opioid dose was also associated with worsening mental health, with more positive PHQ-2 screening, worsening SF-12 mental health score, use of a prescribed antidepressant (for low mood rather than pain) and patient self-reported depression and anxiety.

FSD affected 31.7% of previous opioid users, 35.8% of those receiving <20mg/day of opioids and 50.0% of those receiving ≥20mg/day of opioids. There was increasing odds ratio of FSD with increasing opioid dose when compared with no opioid use but this was not statistically significant (<20mg, unadjusted OR 1.28 (95% CI 0.51, 2.30), ≥20mg, unadjusted OR 2.29 (95% CI 0.94, 5.55)).

Two sensitivity analyses were undertaken that increased the available sample size, the first used STEFFI-2 to identify FSD and the second used medical records data for opioid dose. These returned statistically significant odds ratios for FSD in those taking ≥20mg morphine equivalent dose compared to no opioid use, but this relationship did not remain significant after adjustment with confounders, but the direction of relationship remained with increasing odds of FSD with increasing opioid dose.

10.2 Comparison with other studies

The currently available evidence was synthesised in chapter 3 as part of the systematic review. This included three studies in premenopausal women that

investigated libido. Low libido was found to affect 61-100% of women taking opioids, one paper undertook significance tests but no significant differences were seen between opioid users and controls. These papers all had small numbers of participants (Finch et al., 2000; Roberts et al., 2001; Wong et al., 2011). The cohort study undertaken for this thesis (see chapter 6) found coded low libido in 0.9% (95% CI 0.7, 1.0) of long-term opioid users and 0.7% (95% CI 0.6, 0.8) of short-term users. Cox regression revealed a trend towards an increased risk of low libido with long-term opioid use when compared to short-term opioid use, with an adjusted hazard over 5 years of follow-up of 1.19 (95% CI 0.96, 1.48). None of these analyses were statistically significant.

The most important comparison to draw between the studies is how FSD was defined, as this underpins the remaining comparisons. The studies all used different definitions for FSD, with the cross-sectional study for the thesis being the only one to use a validated measure, and to follow guidelines where distress must be present for symptoms to be classified as FSD (American Psychiatric Society, 2013; Basson et al., 2001; Kriston et al., 2010; McCabe et al., 2016; World Health Organisation, 2012). Wong et al (2011) asked a single question, about whether participants felt their sexual desire had decreased, compared to before their chronic pain or opioid use. Finch et al (2000) report use of a standardised protocol which asked about libido and sexual function, but there was no mention of this being validated and Roberts et al (2001) report using a self-administered questionnaire that asked about adverse effects to opioids, but it is not clear if any of these meet the diagnostic criteria for FSD. The cohort study was based on symptoms of low libido reported by a patient

and recorded in the notes, so will not have followed a validated measure, but if they have been reported are likely to be causing distress.

The cross-sectional study had a prevalence of FSD of 50.0% in opioid users receiving an oral morphine equivalent dose of ≥20mg/day, 35.8% in <20mg/day users and 31.7% in previous opioid users, in comparison with prevalence of low libido of 61-100% in the studies within the systematic review and 0.6-1.0% in the cohort study (Finch et al., 2000; Roberts et al., 2001; Wong et al., 2011). The differences in prevalence between the studies, reinforces the perception that the cohort study underestimated the number of women affected by FSD, and that medical records may not the best way to investigate this area; this is reinforced by results from the medical records review for the cross-sectional study which found no women with a coded diagnosis of low libido in the notes, compared with 50/116 who consented to medical records review who had a positive STEFFI-5 result. The cross-sectional study results are closer to the results of the studies included in the systematic review, particularly the one study that investigated oral opioids and reported a prevalence of FSD of 61% in current opioid users, the remaining studies were using intrathecal opioids and had higher prevalence of 71-100% (Finch et al., 2000; Roberts et al., 2001; Wong et al., 2011). The cross-sectional study may have a lower prevalence of FSD compared to the systematic review papers as the definition for FSD used required symptoms to be accompanied by distress (American Psychiatric Society, 2013; Basson et al., 2001; McCabe et al., 2016; World Health Organisation, 2012). None of the studies included in the systematic review or the thesis (cross-sectional study and cohort study), were able to show a statistically significant difference in FSD between types of opioid use, but with increased

numbers in the sensitivity analysis for the cross-sectional study, a significant result was seen, this indicates that in a well-designed study with larger numbers, the results may have been significant.

Three different methods were used to collect data on FSD across the studies, self-report questionnaire (Roberts et al 2001 and the cross-sectional study), interview (Finch et al 2000 and Wong et al 2011) and database research (cohort study). Asking women about symptoms directly in the cross-sectional study meant that FSD identification was not subject to the clinical iceberg (Last, 1963). It also meant that actual opioid use rather than prescribed dose could be used to calculate daily morphine equivalent dose. However self-report measures are more prone to non-response, the studies included within the systematic review did not report any non-response as the patients were recruited directly from clinic and consent was gained prior to enrolling the participant, so there may have been those who refused to participate in the study but this was not reported. The cohort study was also not subject to non-response as it was based on electronic medical records. The effect of non-response is discussed in depth later within this section. Interviews are more at risk of social desirability bias (where the respondent alters their response based on what they feel the interviewer wants to hear or what they consider to be the expected answer). The risk of this is lower with self-report questionnaires and this was an advantage of the cross-sectional study when compared with the two related studies included in the systematic review.

The cross-sectional study was set within primary care, whereas the papers included within the systematic review were all set in secondary care pain clinics (Finch et al., 2000; Roberts et al., 2001; Wong et al., 2011). This difference in the setting of the

study is important, as only 16% of those suffering from chronic pain in the UK are referred to a secondary care pain clinics, with the remainder managed in primary care (Breivik et al., 2006). The cross-sectional study is therefore more likely to be generalisable to other women prescribed opioids. Additionally, the papers within the systematic review may represent a subgroup of patients, with potentially more severe pain. The cross-sectional study also focused on oral opioids, whereas two of the papers in the cohort study investigated intrathecal opioids. Intrathecal pumps for chronic pain are not routinely commissioned within England, and this further suggests that the results from the cross-sectional study are likely to be more generalisable to the population of interest (opioid users within the UK) than the results from the systematic review (NHS England, 2012).

A recent population based survey in Denmark in 2014 (administered by the National Institute of Public Health) and had a 56% completion rate, compared with a completion rate of 15% for this cross-sectional study (Birke et al., 2018). The response rate for the Danish survey is likely to have been higher than the cross-sectional study response rate as it is a national health and morbidity study undertaken by the National Institute for Public Health. Sexual health constitutes just a small proportion of the survey. Data was collected via face to face interviews and self-report questionnaires which may have increased the response rate further. This study is a long running national study and has itself seen decreasing response rates in young women (Ekholm et al., 2009). Despite the differences, the Danish study found the odds of reporting dissatisfaction with sexual life was increased in all chronic pain patients, and increased further in those patients reporting chronic pain and receiving opioids (OR 1.81, 95% CI 1.23, 2.68) which was of a similar magnitude

as seen in the cross-sectional study reported here (≥20mg/day opioids compared with no opioids OR 2.29, 95% CI 0.94, 5.55) (Birke et al., 2018). Birke et al (2018) did not report on data split by gender, so it was not included in the systematic review. The Danish study did not use a validated questionnaire for identifying sexual dysfunction, whereas the cross-sectional study did use a validated measure. The Danish study used automatically recorded prescription records for opioid use, opioid use was split by duration of use and did not take into account the daily dose of opioids, whereas the cross-sectional study was able to take into account daily opioid dose during the analysis. Including daily opioid dose does appear to be important from the results of the cross-sectional study with an apparent increase in odds ratio for FSD as the daily morphine equivalent dose increased, dose related responses have been seen in previous work on other adverse effects of opioids (Bedson et al., 2019a; Dunn et al., 2010; Saunders et al., 2009).

10.3 Strengths and limitations of the study

One advantage of the cross-sectional study was that it could enquire directly about sexual function, and this was important as the cohort study used medical records and did not identify the expected number of women with FSD. Therefore the cross-sectional study was not affected by the clinical iceberg effect that was likely to have affected the CPRD cohort study (Last, 1963). This resulted in a higher proportion of women appearing to be affected by FSD in the cross-sectional study when compared to the cohort study. Another strength of the cross-sectional study is that the tool for assessing FSD was previously validated, and could be used for all women regardless of whether they were currently in a relationship, or had been sexually active within the preceding year. Including all women was important as women may be excluded

from completing some tools based on lack of recent sexual activity (some tools require women to either be currently in a relationship, sexually active or be heterosexual, which restricts their use), but this lack of sexual activity, could be secondary to FSD, so could potentially affect results (see Table 8-2 for further information on alternative tools) (Kriston et al., 2010).

In order to take advantage of the self-report questionnaire, questions designed for the study had as low a reading age as possible, and this hopefully improved the quality of the responses as the questions were easily understandable and this was checked with a PPIE group prior to sending the questionnaire. Low reading age for the questionnaire was important, as the participants' ability to understand and respond to a question is dependent on their level of health literacy. Any misunderstanding can affect the validity of the data collected (Paz et al., 2009). Previous studies into health literacy have found that 43% of those studied fell below the competency for understanding health related texts, see Section 4.4.5 for further information on health literacy (Paz et al., 2009; Rowlands et al., 2015). Postal questionnaires have a high cognitive burden, and are not usually the preferred method of survey for respondents (they mainly prefer face to face interviews), but postal questionnaires are more likely to yield answers to sensitive questions when compared with face to face interviews (Bowling, 2005).

Another strength of the study was that it was able to assess chronic pain through the use of the chronic pain grade, which has been shown to be comparable to pain diaries (Von Korff and Dunn, 2008). It was then possible to take pain severity into account when assessing the relationship between FSD and opioid use, which was not possible in the CPRD cohort study introducing potential for confounding by

severity. The ≥20mg/day opioid group had the highest proportion of patients affected by the highest chronic pain grade (high disability and severely limiting pain), this is a pattern that has been seen in previous work with those receiving the highest doses of opioids having the severest pain, poor health related quality of life and poor physical function (Sjøgren et al., 2010; Turner et al., 2015). Opioid prescriptions would be expected to be correlated to pain at baseline but if they were helping with pain and function you would expect pain grade to decrease, this fits with previous evidence that has not found evidence for opioids effectiveness in long-term pain. Those women receiving the highest doses of opioids reported the highest amount of pain. Physical health was also taken into consideration during analysis, which was a strength of the study given that increasing opioid dose was associated with worsening physical health (e.g. increasing opioid dose associated with decreased SF-12 physical health score and increasing BMI). However these confounders could only be included as a single confounder at a time rather than building a full multivariate model for the logistic regression due to low response rate.

Another strength of this study was having direct information about daily dose of opioids, but this also meant that there was the potential for missing data when patients did not complete these sections. Indeed, this item had the largest amount of missing data, which was a limitation introduced through using a self-report measure. However it was possible to categorise 135 (of 146) into either no opioid use, <20mg, or ≥20mg/day morphine equivalent dose of opioids based on the information provided (and a further nine participants could be assigned to a group following medical records review and this was able to be used as a sensitivity analysis). Self-reported information on medicines (particularly analgesics) was important, as

prescription records may not reflect actual usage, due to over-ordering, diversion of medicine (opioids in particular have the potential for abuse), or because a medicine was not used as prescribed. Analgesics are particularly prone to these issues as they are variably used according to pain level. All of this means that it was an advantage to have information on actual usage of opioids, as daily morphine equivalent dose was able to be confidently calculated and used in analysis.

In order to create a homogenous group for analysis, and for the cross-sectional study to be comparable to the cohort study, women with musculoskeletal conditions and an opioid prescription within the preceding six months were identified for inclusion. Of those who responded, only 39.7% indicated joint pain (all locations), with this rising to 60.4% in ≥20mg/day opioid users, and dropping to 12.2% in previous opioid users (this was a statistically significant difference). This is a limitation as not everyone identified as having painful joints, even in the highest dose opioid group, so the sample may not represent the population of interest, however it could indicate that the treatment was effective and the pain had resolved with treatment. This lower prevalence of joint pain is likely due to women with a musculoskeletal problem being identified over the preceding six months (as pain may have resolved particularly in those currently not using opioids), however those using opioids currently who do not self-report joint pain, must either have missing data for this item, currently be having a period where their joints are not causing a problem, the opioid is working to control their pain, or be using analgesics for a different reason.

Another advantage of the cross-sectional study was the ability to take into account contraception. Women were separated into two groups based on contraception use into hormonal contraception and non-hormonal contraception/no contraception use

and this was adjusted for during analysis. This was an important step as hormonal contraception can affect sexual function, and the study population included only women of childbearing age. In 2008/9 74% of women under 50 years were using at least one form of contraception and 12% of women were using no contraception and were sexually active (Lader, 2009). Adjustment for hormonal contraception use decreased the odds ratio for FSD but did not change the direction of relationship with increasing odds of FSD with increasing opioid dose.

Despite the overall unit response being low, the item response was good, which was a strength since it meant that of those that responded, the data for the majority could be included in the analysis and preserved the sample size achieved. Importantly only two women did not complete the sexual function tool and only 12 had item missing data for this tool that affected the result of STEFFI-5. One strength to using the STEFFI-5 tool, was that STEFFI-2 is embedded within it, and when this was used only seven women had not given enough data, this could then be used for a sensitivity analysis, this increased the sample size and results became significant. This good item response was likely to be due to the mode of delivery of the survey, with high item response for sensitive topics often seen in postal self-report questionnaires likely to be due to the pseudo-anonymity offered (the practices had lists linking the participant to their study number but did not have access to any of the completed questionnaires and the study team did not have access to patient identifiable data) by this method study (Bowling, 2005).

11 responders did not provide enough medicine information to be put into an opioid group for analysis which was a weakness as it decreased the sample size available for analysis and therefore the statistical power. However, nine of these women could

be put into a group following medical records review and this was used for a sensitivity analysis. Item non-response was higher in those who did not report current opioid use and could be related to how pertinent they felt the study was to them. Six (14.6%) previous opioid users did not complete information on medical history, this might be due to skipping the question, or that they did not have any conditions but did not choose the 'none of the above option'.

A further strength of the survey was that mental health of the participants could be taken into account. This was important as mental health is related to sexual function (Ambler et al., 2001; Gracia et al., 2004; Hayes et al., 2008). Pain, mood and disability have all been shown to be related to sexual function in patients with chronic pain (Ambler et al., 2001). Mental health was assessed through PHQ-2, SF-12 mental health component and participant self-report, therefore mental health could be assessed without the need for the participant to have a diagnosed mental health condition. Worsening mental health (PHQ-2 screen, SF-12 mental health score, use of an antidepressant and self-reported anxiety or depression) was associated with increasing opioid dose and this was statistically significant. It appeared from the analysis, that the SF-12 mental health component had the largest effect on the relationship seen between opioids and FSD, but this did not completely change the direction of relationship just decrease the magnitude. PHQ-2 scores correlated well with those participants who self-reported depression and anxiety but not with antidepressant usage.

Another strength of the study was the ability to use the information on all of the above factors (mental health, chronic pain grade, contraception) and compare the groups within the study and take these into account as possible confounders which improved

the internal validity of the study. Unfortunately due to the low numbers multiple regression with all relevant factors could not be undertaken and this was a limitation of the study.

A final strength of the study was that important confounders, including medicine use and demographics were also taken into account. It was important to include other medicines in the analysis as increasing opioid use was associated with polypharmacy and increased use of non-opioid analgesics (including gabapentoids and antidepressants) and these factors could potentially act as confounders. The opioid groups were also comparable in terms of their demographics, including ethnicity, and were only statistically significantly different for employment

The main limitation with the cross-sectional study was the low response rate with only 15% of those invited responding to the survey. This can affect results in several ways, for instance decreased sample size increases the risk of non-response bias, which therefore affects the external validity and generalisability of the results (Bowling, 2005). The target response rate was 31.6%, so the achieved sample size is less than half the response rate that was expected.

As discussed above only univariate analysis could be performed rather than multivariate analysis where opioid use was controlled for with only one other important factor. This was to a certain degree reassuring, as the direction of relationship remained constant when adjusted for individual confounders. However, the complex relationships between multiple variables was not accounted for, and residual confounding remains a potential issue within the study. In this way, the low response rate has affected the ability to draw conclusions from the survey. The decreased power has also meant that even though there is a visible direction of

relationship and an apparent dose response, this was not statistically significant and it is not possible to say whether this is because the relationship between opioid use and FSD is not significant or if it is due to the low numbers included in the analysis. The sensitivity analysis suggests that the lack of relationship seen was more likely due to decreased sample size and power, rather than due to an absence of relationship.

Non-response bias is the next concern introduced through the low response rate. Previous work has shown that the participation rate does not determine the extent of non-response bias, and that participation rate is only weakly associated with presence of bias (Galea and Tracy, 2007). Non-response bias is introduced when those who respond are systematically different to those who do not respond, particularly if these characteristics are important to the study outcome. That said the lower the response rate, the higher the risk that responders and non-responders will differ systematically (Bowling, 2005). The responders and non-responders could only be compared for age and deprivation (based on practice postcode), and they were statistically significantly different for both factors, with responders being older, and from less deprived areas. The limitation with this comparison is that social deprivation was based on postcode of the practice, and there is evidence that this method underestimates level of deprivation in less deprived areas and overestimates deprivation in more deprived areas (Strong et al., 2007). This may have particularly affected participants from the largest practice, which had over 40000 registered patients, and therefore a single postcode is unlikely to reflect the diversity of these participants. The fact that respondents were from less deprived areas may have introduced bias, as from the responses it appears that responders from practices in

more deprived areas, were more likely to be prescribed opioids than those in less deprived areas, which could introduce a systematic difference in the sample for instance lower socioeconomic status in childhood has been shown to be related to obesity in adulthood (Bann et al., 2017).

This study is consistent with previous studies into sexual health that have found those from areas with lower levels of deprivation are more likely to respond (Malavige et al., 2015). Health literacy is often associated with level of deprivation, so this may reflect why those from higher areas with less deprivation were more likely to respond, as postal questionnaires place a high burden on the respondents ability to read and understand the questions (Bowling, 2005; Rowlands et al., 2014). The difference in age between responders was statistically significant, but it represented a small difference in actual age with the median age in responders being 38 years old (IQR 31-42) and non-responders 35 years old (29-41). This difference in age is unlikely to have affected the results, and previous studies in premenopausal women have not found age to be significantly associated with low libido (Gracia et al., 2004). These differences between responders and non-responders may also have affected the generalisability of the results as the population of interest may not be represented by those who responded and this in turn affects the external validity of the study (Bowling, 2005; Galea and Tracy, 2007).

Another factor that may have introduced non-response bias is that the response rate can be affected by salience (relevance of the subject to those invited to participate) (Galea and Tracy, 2007). In the case of the cross-sectional survey this could be a drawback, and may have affected the results in several ways. Women who have FSD may have been more likely to respond, which could inflate the prevalence of

FSD in the study group, however this is likely to have a similar effect across the whole group and not just one group of opioid users. Women who were not currently sexually active, or not in a relationship may have chosen not to participate, which could be a systematic difference between responders and non-responders. There is no data on the marital status of non-responders but responders can be compared to the data from the 2011 census (the census does not include co-habiting in its relationship types whereas the cross-sectional study does). In the census 46.6% of adults in England were married compared with 48.0% within the survey. 34.6% of those within the census identified as being single compared with 21.9% within the study, however a further 21.9% identified as cohabiting and this would be included within the single category for the census data (Smith, 2014). This comparison seems to show that it is unlikely there was a systematic difference between responders and non-responders based on relationship status, which suggests that this was not a factor that affected response and therefore there is unlikely to be bias secondary to relationship status. There was also no statistically significant difference between the opioid groups or when the participants were split by FSD in terms of relationship status, which is reassuring and suggests this did not limit the study.

It is important to consider the possible reasons for the low response rate. The estimated response rate was 31.6%, but this was based on historical data from 1998 and this study was also completely anonymous whereas this study was only pseudo-anonymised (Dunn et al., 1998). The reason for using this data was because it represented a local population (geographically similar to the recruiting area for the cross-sectional study), receiving a completely unsolicited population survey with a focus on sexual health. In comparison to this, the overall response rate to the cross-

sectional study was 15%, with some practices having no responses and some having a response rate of over 30% approaching the original estimate. It is likely that this response rate (15-30%) actually reflects a more realistic view of the response rate that should have been expected, given the decrease in response rate since this questionnaire was sent and the personal nature of the questions (Galea and Tracy, 2007; Morton et al., 2006). A more recent study in men examining sexual health, that requested consent prior to sending questionnaires had a recruitment rate of only 8.8% and of those recruited 71.5% responded to the questionnaire, which is an overall 6% (544/9100) response rate (Malavige et al., 2015). If the response rate to the cross-sectional study is compared to the response rate of Malavige et al. (2015) then it seems to be a reasonable response rate, however when compared to the Danish study discussed earlier in this chapter with a response rate of 56% it would seem very low, the differences for this were discussed earlier (Birke et al., 2018; Malavige et al., 2015). It is clear that if the participants had been contacted about the study first there would have been a lower amount of non-response to the survey itself, however patients would then have consented to be included so selection bias may have been introduced.

Factors that could have affected the response rate are the increasing number of surveys that patients are sent, decrease in volunteerism, request for medical records review, requesting future contact as part of the study, age of the population of interest and mode of the survey (Bowling, 2005; Dunn et al., 2004; Galea and Tracy, 2007; Green et al., 2018). Requesting consent for medical records review and future contact can decrease response rate, perhaps due to the perception that this will increase the burden of the research. It has been found in general that those who

consent to medical records review are likely to be younger (reaching a peak at 40-49 years old) and more likely to have the condition of interest (Dunn et al., 2004). There were no significant differences between those who consented for medical records review, and those who did not consent for medical records review in terms of social deprivation or age. A recent population face to face survey on a non-sensitive subject found that response rate increased in women up to 67 years old then began to decrease again (Green et al., 2018). The response rate in this study ranged from 28% in 18-27 year olds up to 37% in 38-47 year olds and this was undertaken in 2011, so it appears that the response rate could have been increased if the study had been undertaken as face to face interviews rather than a postal questionnaire (Green et al., 2018). Responses to sensitive questions may have been affected by altering the mode of survey, as the interviews would have had an increased risk of social desirability bias (as participants are in direct contact with the interviewer and are more likely to take into account social expectations when responding to a sensitive question), which can particularly affect research into sensitive subjects (Bowling, 2005).

10.4 Meaning of the study

As in all cross-sectional studies associations can be reported but characterising the direction of relationship is more difficult. Bradford-Hill (1965) developed a set of rules for determining whether a relationship is likely to be an association or causation. Bradford-Hill's rules include considering the following factors that characterise the relationship; strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy, these factors do not demonstrate causality but they are a useful guideline for when considering an association

(Bradford-Hill, 1965). The relationship seen in the results from the cross-sectional survey did not reach statistical significance (except in the sensitivity analysis), but it still meets some of the above criteria for a causal relationship, suggesting further investigation is required.

The logistic regression appeared to show a dose response relationship, with the odds of FSD increasing with increasing daily morphine equivalent dose. Previous work has found significant relationships between increasing daily morphine equivalent dose and adverse effects (Bedson et al., 2019a; Dunn et al., 2010; Saunders et al., 2009). The relationship between opioids and FSD appears to be consistent with recent studies observing similar relationships between opioids and sexual function in different populations (Birke et al., 2018). The strength of the relationship seen is the next criteria to consider whether the relationship is plausible. The results of the cross-sectional study show that women taking a morphine equivalent dose of ≥20mg/day had around double the odds of FSD when compared with those not currently taking opioids. This relationship remained in the same direction even when adjusted for individual confounders. The relationship seems to be consistent and has been seen in different CNCP populations receiving opioids, most recently in a whole population study in Denmark (Birke et al., 2018).

The specificity of the relationship is more difficult to assess. FSD appears to affect a large proportion of the population, and as discussed previously there are many factors that appear to contribute to this, since CNCP, opioid use, mood and FSD appear to be closely interlinked (Arunakumari and Walker, 2009; Hayes et al., 2008). It is difficult to determine whether the relationship seen is specific to opioid use rather than one of the other factors, as multiple logistic regression was impractical due to

low numbers. The relationship between FSD and opioids appears to remain following adjustment for CNCP and this has also been seen in previous research where both CNCP and opioid use have effects on sexual dysfunction independently (Birke et al., 2018).

Temporality is difficult to assess in this case due to the cross-sectional nature of the study. The relationship appears to be biologically plausible and related to the affect that opioids have on HPG axis, where decreased hormone levels can lead to sexual dysfunction and affect menstrual cycle (Vuong et al., 2010). Coherence is important and the results do not conflict with any widely received scientific wisdom and is in fact in keeping with the available literature even though this is currently sparse (Wersocki et al., 2017).

Following an analysis of the relationship seen with Hill's criteria, it would seem that it would be acceptable to cautiously suggest that there is a potentially causal relationship between opioids and FSD. Clearly, however, it is necessary that further investigation to elucidate the direction of relationship is required, and it is likely that this would need to be part of a wider RCT into opioid effectiveness and adverse effects, or alternatively a cohort study examining the benefits of withdrawing opioid therapy in a structured and supported manner.

Pain grade and opioid use were associated with one another (increasing pain grade was associated with increasing opioid dose), this could potentially mean that there is confounding due to chronic pain itself (confounding by indication, see section 4.7.3). The adjusted odds ratio, adjusting for pain grade, showed the same direction of relationship between opioid use and FSD, and only a small change in the odds ratio for FSD, and in the sensitivity analysis using medical records data the odds ratio

remained statistically significant when adjusted for chronic pain grade. With increasing dose of opioid pain grade would be expected to decrease, however this is not the case in the cross-sectional study and previous work has shown, that increasing opioid dose is associated with increased pain and decreasing physical function (Green et al., 2013). There is also evidence for a particular adverse effect known as opioid induced hyperalgesia, which can cause the patient to become more sensitive to certain painful stimuli, thereby worsening pain, the prevalence of this is unknown but it could be playing a role in the increased pain seen in those using more opioids (Lee et al., 2011).

There was a range in proportion of those included in the study from each practice (0.12-0.92% of the practice list), there is no way to interpret this further without more information on the demographics of the patients registered at each practice. This difference in proportion may reflect different proportions of women in the age group on the practice lists, number of those registered who have a musculoskeletal condition or the differential prescribing of opioids in each practice. There is an 8 fold difference in the numbers meeting the inclusion criteria between different practices, it is unlikely that the numbers in the age groups vary by this amount, so the difference is likely to reflect somewhat different prescribing practices between clinicians and practices.

90.4% of the population reported their ethnicity as being White. This is higher than the proportion in the general population, with 86% of those in the 2011 census in England and Wales reporting they were White (Office for National Statistics, 2012). In Staffordshire Moorlands (one of the recruiting areas), the proportion of those reporting they were White rose to 97.5% (one of the top three areas within England

and Wales). The sample has a slightly higher proportion of women reporting their ethnicity as White when compared to the general population, but lower than the rates than in Staffordshire Moorlands. The sample overall appears to be representative in terms of the UK populations ethnicity.

Finally there was a group of women on opioids, using no contraception but having sexual intercourse. There is no data on whether this is with partners of the same or opposite sex, so it is not clear if these women are at risk of pregnancy. Opioids are not recommended during pregnancy, unless the benefits outweigh the risks (and they should be prescribed at the lowest possible dose if used), and this is particularly important in this group of women as they are all of childbearing age (BNF, 2018a). The British Pain Society (2010) recommends changing opioids to an alternative prior to conception if this is possible due to the risks of withdrawal symptoms in the baby at birth (The British Pain Society, 2010). It is worthwhile considering whether contraception is important to discuss with these women when commencing opioids, and at medicine reviews and indeed whether it is appropriate to start opioids in the first place.

This study adds further evidence for adverse effects related to opioid use and supports that this relationship appears to be dose dependent as found in previous studies (Bedson et al., 2019a; Dunn et al., 2010; Saunders et al., 2009). As discussed previously opioid use has increased over the last 20 years (Bedson et al., 2016; Foy et al., 2016). With the growing body of evidence to show that opioids have significant adverse effects this needs to be taken into account and careful consideration taken prior to prescribing opioids and in those who are already

receiving opioids, escalation should be avoided if possible and opioid dose de-escalated (British Medical Association, 2017).

10.5 Further research

The cross-sectional study was unable to show statistically significant results, but did show a direction of relationship, with increasing dose of opioids associated with increased odds of FSD, and these results became significant when sensitivity analyses were undertaken which included up to nine more women. The study would ideally be repeated with larger numbers. One way to increase the response rate would be to include sexual function questions within a larger study, where the questionnaire is not the first contact with the participant. Previous studies that have included sexual function questions within larger questionnaires seem to have better response rates (Birke et al., 2018). Due to low numbers it was not possible to adjust for multiple factors in logistic regression so there is a chance that results are actually secondary to a confounder. This means that the study needs replicating with larger numbers.

There may be a safe level of daily opioid dose for these adverse effects; future research should include daily dose as well as current opioid use. If a safe daily morphine equivalent dose was identified then treatment trials of opioids in patients could be undertaken with doses only escalated up to this safe level. This would mean that opioids could be trialled safely and only continued if effective for pain with less risk of adverse effects.

This study intended to investigate whether there was any difference in risks of FSD dependent on the mode of delivery for the opioid. However this was not possible as

only two participants were receiving transdermal opioids. It would be important to study this further in the future to assess whether any specific opioids or modes of delivery are safer than others. Previous work on cardiovascular risk associated with opioids found that some opioids were associated with different levels of risk (hydrocodone was shown to have lower all-cause mortality at 30 days when compared to codeine and oxycodone) (Solomon et al., 2010a).

This study did not investigate levels of hormones as it was a non-experimental study. It would be interesting in the future to investigate levels of HPG axis hormones (LH, FSH, oestrodiol, progesterone and testosterone) and how they change in relation to opioid use to determine whether these can be used as early markers for FSD.

10.6 Key messages

There is a high prevalence of FSD, within the cross-sectional study. This highlights the importance of women being asked about sexual function during medicine reviews, and this being discussed with women as a potential adverse effect prior to prescribing opioids. There was no statistically significant difference between groups of opioid users for FSD but there did appear to be a direction of change, with the odds of FSD increasing with opioid dose. The lack of statistically significant results is more likely to reflect the low numbers, rather than a lack of relationship, which is supported by the sensitivity analyses which included more women and found a statistically significant relationship. Given the relationship appears to be dose related, there may be a safe dose level at which these medicines can be prescribed. Further work would be required to delineate a safe dose of opioids and this may be different

between patients. For current use it would seem that if opioids need to be used they should be used in the lowest possible dose and only if effective.

Increasing doses of opioids were associated with worsening pain, physical and mental health. It is impossible to say whether this was due to opioids, but women receiving the highest doses appear to have the worst overall health.

It is important to discuss contraception with women when they are being prescribed opioids, as they are not recommended during pregnancy unless the benefits outweigh the risks.

10.7 Conclusion

The cross-sectional study has shown a much higher prevalence of FSD than the CPRD cohort study. FSD affects a large proportion of women with musculoskeletal pain who have been prescribed opioids. The study did not show a statistically significant relationship between daily opioid dose and FSD, there was an increase in the odds of FSD with increasing daily dose of opioids, with women taking ≥20mg/day morphine equivalent dose having double the odds of FSD when compared to those not currently using opioids. Despite no statistically significant relationship, since FSD was reported in 44% of women, it is important that this is discussed when considering prescribing opioids to women with musculoskeletal pain.

The study was limited by the low response rate, and this has affected the ability to draw a strong conclusion. The cross-sectional study has, however, added useful information to the current body of evidence in this area.

11 Discussion

11.1 Thesis summary and main findings

This thesis has focused on investigating the possible relationship between opioid use in women with chronic non-cancer pain (CNCP), and female sexual and reproductive dysfunction. The main focus of the thesis has been investigating patients with musculoskeletal pain as the cause for CNCP. Chapter 1 introduced the subject and set out the aims and objectives for the thesis.

Chapter 2 focused on the background to the studies included within this thesis, this included definitions of pain, opioids and the relevant parts of the endocrine system and the epidemiology of CNCP, opioid use and opioid adverse effects. The rationale for investigating female reproductive and sexual dysfunction further is outlined. It was concluded that this was an area that required further investigation, and additionally this had been highlighted as such by the British Pain Society (The British Pain Society, 2010).

Chapter 3 investigated the currently available evidence using a comprehensive systematic review of the literature. The systematic review included 12 papers with 165 cases and 35 controls. The review supported the hypothesis that there is a link between opioid use and reproductive and sexual dysfunction but did not provide any definitive evidence. The results of the systematic review, therefore, established the need for further investigation of this area.

Chapter 4 discussed the methodology underlying the studies undertaken throughout the remainder of the thesis, highlighting both the strengths and weaknesses of each approach.

Chapters 5, 6 and 7 described and discussed the database cohort study that was undertaken for this thesis. The cohort study compared long-term to short-term opioid use for four outcomes: menopausal symptoms/menopause, abnormal menstruation, low libido and infertility. The cohort study included a large number of women (over 40,000), split evenly between short-term and long-term opioid users and found an increased risk of menopausal symptoms/menopause (HR 1.16, 95% CI 1.10, 1.23) and abnormal menstruation (HR 1.13, 95% CI 1.05, 1.21) in women prescribed long-term opioids when compared with short-term opioids. The results relating to low libido and infertility were non-significant. Low libido appeared to affect more women in the long-term opioid group, compared to the short-term opioid group but the total number affected (0.8%) was lower than expected when compared to population estimates (25-41%) (Dunn et al., 1998; Laumann et al., 2005). Given this discrepancy in the number of women affected by low libido between the cohort study and general population estimates, it was determined that an alternative method was needed to investigate this area.

Chapters 8, 9 and 10 describe and discuss the cross-sectional postal survey that was undertaken for the thesis which investigated female sexual dysfunction (FSD) further. An invitation and postal questionnaire were sent to over 1000 women with a response rate of 15%. Responders were split by daily morphine equivalent dose (0mg/day, <20mg/day and ≥20mg/day) and compared for FSD (assessed using STEFFI-5 tool) and other factors (including age, chronic pain grade and medicine use). The prevalence of FSD within the cross-sectional study was 39.3% overall; 31.7% in those not currently taking opioids, and 50.0% in those receiving a morphine equivalent daily dose of ≥20mg/day. There was increasing odds of FSD with

increasing opioid dose (0mg/day (reference group), <20mg/day (1.28, 95% CI 0.51, 3.20) and ≥20mg/day (2.29, 95% CI 0.94, 5.55)) but the results were not statistically significant. Two sensitivity analyses were undertaken and the odds ratio for women taking ≥20mg/day morphine equivalent today became statistically significant in both.

This thesis adds to the current literature as it was able to confidently identify the lack of current evidence in this area through the systematic review. The cohort study was, the first large scale cohort study investigating this area and found increased hazards for two of the outcomes included (menopause and abnormal menstruation) in those women prescribed long-term opioids. The cross-sectional study adds to the literature as it indicated that there is a potential dose dependent relationship between FSD and opioid use, which may stimulate future research to investigate whether there is a safe dose at which opioids might be prescribed in pre-menopausal women.

11.2 Strengths and limitations

11.2.1 Strengths of the thesis

The work undertaken for this thesis fills a clear gap identified in the evidence for sexual and reproductive dysfunction in women prescribed opioids and was the first to undertake a large cohort study in this area. A major strength of this thesis is that the investigation of the overall aim was undertaken using three different study designs. This allowed for comparison of the results and triangulation to assess if the results converged with one another. The systematic review supported the hypothesis, that there was a relationship between opioids and reproductive and sexual dysfunction in women under 55 years old but did not provide the depth of evidence to draw a firm conclusion. The results of the subsequent studies undertaken for the thesis

strengthen the conclusions drawn from the systematic review, adding detail and estimates of effect. The results from the three studies converged to indicate that there is a relationship between opioid use and reproductive and sexual dysfunction and thereby increases the confidence in the results of each individual study (Heale and Forbes, 2013). The use of multiple methods was particularly a strength for investigating FSD which was exemplified by the difference in prevalence of low libido between the cohort study (<1%) and the cross-sectional study (39.3%). The results of the cross-sectional study were more in keeping with previous studies included within the systematic review and of the general population where a recent meta-analysis estimated a prevalence of 41% (Dunn et al., 1998; Laumann et al., 2005; McCool et al., 2016). This highlights the strength of using a cross-sectional self-completed study for investigating FSD, and the limitations of investigating FSD in a database, which is discussed in further depth in the next section and the importance of using more than one study design to answer the questions within this thesis.

A further strength of the cohort study, and cross-sectional study, was that they were undertaken in a primary care setting. This is important because the majority of opioids within the UK are prescribed by GP's in primary care, with only a small number of people referred to specialist pain clinics (Breivik et al., 2006). It is significant that the studies are set in primary care, as they are more likely to provide results that are generalisable to the population of interest from within the UK since over 98% of the UK population is registered with a GP (Herrett et al., 2015). Within this thesis the population of interest (those prescribed opioids) would have all been registered at a GP, as this is the only way in the UK to access regularly prescribed medicine. Consequently, this means the sampling frame should be appropriate. The

full benefits and disadvantages of CPRD have been discussed previously in the thesis (see sections 4.6 and 5.4 for full details) and importantly it has been shown to be comparable to the UK population (Herrett et al., 2010).The identification of the participants was undertaken using a comprehensive list of Read Codes (including symptoms and diagnostic codes) that were developed within the research centre by experts (including primary care clinicians) in musculoskeletal research. It is therefore unlikely that any women presenting with musculoskeletal conditions will have been omitted from the studies. The Read Code lists were also checked by ER who is a primary care clinician prior to undertaking the searches for the cross-sectional study. This also strengthens the generalisability of the results as all relevant women are likely to have been identified.

An additional strength of the studies was that all women who met the inclusion criteria were included in both the cohort study (from CPRD population) and the cross-sectional study (from 29 GP Practices).The advantage of this is that there was a reduced risk of selection bias at the initial stage of the studies.

Another strength of the studies is that they split opioid use based on definitions already in use within the literature, which enables to results to be comparable to the evidence already available for other opioid adverse effects. The cohort study split opioids by duration using definitions employed by Von Korff et al (2010), and the cross-sectional study split opioid dose at 20mg, which has also been previously used (Dunn et al., 2010; Von Korff et al., 2008). Using predefined opioid groups means that the results are more directly comparable with the existing body of evidence relating to opioid use and adverse events. If the studies were to be repeated again it would be interesting to split opioids in both studies based on duration and daily

morphine equivalent dose particularly in the cohort study which only considered duration of use.

Research into FSD often only includes women who have been sexually active within the preceding year. This can artificially lower the prevalence of FSD through selection bias, as those women who are not sexually active may have avoided sexual intercourse due to sexual problems (Laumann et al., 1999). A strength of the cross-sectional study is that all women receiving opioids for musculoskeletal pain were included within the target populations regardless of their current sexual activity, and therefore this particular form of selection bias is avoided.

11.2.2 Limitations of the thesis

As discussed within section 11.2.1 there were limitations associated with investigating FSD in the cohort study. The prevalence of FSD was much lower than expected when compared to population estimates and the results from the cross-sectional study. This comparison supports the view from the cohort study discussion (Chapter 7), that the low prevalence in the cohort study was likely to be due to the clinical iceberg (where women might be suffering from these symptoms but did not present to medical services) (Last, 1963). This can be a limitation of database research, as the absence of a coded diagnosis is taken as the absence of a condition. This is interesting as the women in the cross-sectional study who were identified as having FSD experienced distress secondary to the symptoms, which would lead to the assumption that they would be more likely to seek help. Previously the possible reasons why women may not seek medical attention for reproductive and sexual symptoms have been discussed (section 7.3), this may be due to the perception that they are a private matter, or embarrassment from either the patient or

the clinician about discussing these conditions (Delgado-Rodriguez and Llorca, 2004; Montgomery, 2008). It also seems clear from this comparison that database research is not the ideal way to investigate FSD currently. The low prevalence of low libido in the cohort study, may also have been due to detection bias, where libido may have been one of many complaints, so it was either not coded, or was added within the free text comments, and therefore could not be identified within database searches based on Read Codes. Symptoms that are part of the presenting complaint, but not what the GP considered to be the main issue are often not coded, and even if low libido was coded this may not have followed diagnostic criteria (Jordan and Croft, 2008). Use of databases may be appropriate in the future for investigating low libido if free text information is also included in the search. Previous research around presenting symptoms of bladder and pancreatic cancer found that restricting searches to Read Codes underestimated symptom frequency and potentially introduced detection bias (Price et al., 2016).

An important potential limitation of the studies was the question of hormonal contraception and whether it was included as a confounder within analysis. The cross-sectional study was able to gather information on contraception use, whereas the cohort study was not, due to the nature of how contraception is provided in the UK (this was previously discussed in chapter 7). It was assumed that contraception use would not be different between the two opioid groups when analysing the cohort study. The results of the cross-sectional study found no statistically significant difference between the comparison groups and which type of contraception (if any) they were using. The samples for the two studies were drawn from slightly different populations, with the cohort study coming from CPRD which covers the whole of

England, and the cross-sectional study population deriving from the West Midlands only. Additionally, the comparison groups were different (split by duration in the cohort study and total morphine equivalent dose in the cross-sectional study). The difference in the two populations' means, that the cross-sectional study results cannot confirm that there was no difference in contraception use between opioid groups in the cohort study, but it does provide supporting evidence, that this assumption seems to have been appropriate. However the cross-sectional study was unable to include contraceptive use as a confounder within multiple logistic regression due to low response rate, so it cannot be definitely said that it would have no effect on the results. There were women within the cross-sectional study, who were receiving opioids that were sexually active and not using any form of contraception. This may indicate that women are not aware that opioids are potentially harmful in pregnancy and therefore supports the notion that it is important to discuss contraception with women during prescribing and when reviewing the use of opioids.

Ethnicity was important to consider within the studies as there is conflicting evidence that ethnicity can have an effect on FSD. Unfortunately, 29% of the ethnicity data was missing in the cohort study and this was not adjusted for within the analysis. In the cross-sectional study there was no missing data for ethnicity, but multiple regression could not be undertaken due to the low response rate to the survey overall, which decreased the power available for analysis therefore making this a potential limitation. The cross-sectional study did not find any statistically significant difference in ethnicity between the opioid groups, but a slightly higher proportion identified as White when compared to census data for England and Wales (see

section 10.4) (Office for National Statistics, 2012). As ethnicity was not included within the statistical analysis and was not the same in the cross-sectional study as in the general population, it is not possible to determine whether this is likely to have affected the generalisability of the results. Additionally it brings into question whether the results are applicable to other populations with different ethnicities. Previous work has not reached consensus regarding ethnicity and FSD with some studies finding no difference in odds of FSD occurring in different ethnic groups, whereas others have found increased odds of FSD in those of Black ethnicity and decreased odds in Hispanics when compared to those of White ethnicity (Gracia et al., 2004; Laumann et al., 1999, 2005).

The question then arises as to whether this potential difference in FSD between ethnicities is due to a biological difference or a societal difference. Gracia et al (2004) undertook a study set in the US comparing ethnicity and found no differences in FSD, whereas Laumann et al (2005) undertook a multinational study and compared people from different countries (but did not explicitly include ethnicity in the analysis) and found the highest prevalence of FSD in women from Southeast Asia, East Asia and the Middle East (Gracia et al., 2004; Laumann et al., 2005). There is evidence from previous studies that Hispanic women reproducibly underreport FSD, so there appears to be potential for women from different cultures and ethnic backgrounds to answer questions around FSD differently (Laumann et al., 1999). Research has investigated if cultural issues can affect the reporting of FSD, and whether the gender balance of a culture can have an effect. The lowest rate of FSD was in the non-European West (32.1% 95% CI 21.1, 44.4), and the highest rates in Africa (61.7%, 95% CI 48.6, 74.0) (McCool et al., 2016). There is no clear biological evidence to

suggest that those from different ethnicities have different levels of adverse effects related to opioids, but there is evidence that drug metabolism varies with ethnicity and this may have implications for adverse effects. The clearest evidence for differences in metabolism are related to codeine, which is metabolised by CYP2D6 (an enzyme primarily expressed by the liver) to the active metabolite morphine. CYP2D6 broadly has two different phenotypes split into poor metabolisers and extensive (normal) metabolisers. The level of poor metabolisers varies dependent on ethnicity with 7.2% (3.2, 10.7) of White people in studies identified as poor metabolisers falling as low as 0.5% (0, 2.1) in those of Asian descent. Those who are poor metabolisers will not be able to convert codeine to its active metabolite, and therefore will gain no benefit from codeine, and also appear to have less adverse effects (Burroughs et al., 2002). There is therefore evidence that potentially ethnicity might affect the rates of adverse events, particularly for codeine (which was used by the highest proportion of the cross-sectional study), and with those of White ethnicity being less likely to have adverse events. This is therefore a potential weakness of the studies, and may limit the applicability of the results in other populations with different ethnicities, perhaps overestimating the prevalence of adverse effects. The results should, however, be generalisable to the general population within the UK.

One difficulty with investigating FSD is the multiple definitions used and consequently determining a single definition and assessment tool to evaluate this (discussed in Section 2.5 and 8.7.1). This means that the three sections of the thesis have used different definitions of FSD which are therefore not directly comparable, thereby introducing some limitations when comparing the results. The systematic review included studies that identified FSD based on symptoms, none of the papers

reported using validated measures to diagnose FSD. The cohort study only identified women who a GP had coded with low libido (this is unlikely to have followed any diagnostic criteria), and the cross-sectional study used a pre-validated measure that considered the diagnostic guidelines for FSD. This is a problem not just for this thesis but for all research relating to FSD as there are multiple definitions and validated measures in current use. The cross-sectional study used the most robust method for identifying FSD therefore the other results should be interpreted in light of this. There is unfortunately no current gold standard for diagnosing and identifying FSD, but an appropriate tool for the study was selected through careful consideration of the assessment tools.

The most obvious limitation within the thesis was the low response rate to the cross-sectional study which has been discussed at depth in Chapter 10. It is important to reflect that this low response rate has affected the ability to draw an overall conclusion from the thesis regarding FSD, as the cross-sectional study was the only part of the thesis to use a validated measure for identifying FSD. If the cross-sectional study were to be repeated it would be important to attempt to maximise both item and unit response rate. Unit non-response could possibly have been increased, for instance, with a telephone contact either prior to sending the questionnaire or following non-response. Telephone contacts were not included within the protocol, due to both economic and logistic reasons, however using this method in future studies would be appropriate. In terms of item non-response there are also specific changes that it would be sensible to make to the questionnaire following having examined the pattern of responses to individual items. The first changes would be to the medicine section where having two separate response lines

for the name and dose of drug, rather than one for both, would make it more explicit that both are required, additionally, including space for five analgesics rather than four, and including space for double the amount of other medicines (participants still reported all their medicines in two lines in the provided space, but it would be better if this were formalised) would have improved data collection. In the other conditions section, one question asked if the participants suffered chronic pain, and there was a poor correlation between the answers to this and the responses to the chronic pain grade results. The reason for this difference is likely to be due to a misunderstanding with respect to the word ‘chronic’, which means a long-term illness to doctors. However ‘chronic” can mean a severe illness to patients (Rowlands et al., 2014). In retrospect it would have been better to change this option to an alternative such as long-term pain (although this would need to be defined), or persistent pain. The difference between those who indicated chronic pain, and those with a high chronic pain grade score may also reflect that some participants simply do not consider themselves to have chronic pain even though they score as such on the validated tool. The final change to the questionnaire that would be adding a further option in the question surrounding current employment status whereby the option “employed but currently off sick” would be altered to encompass those on disability benefits, this is due to the number of women who ticked other in the questionnaire and in the description wrote that they were currently on disability benefits. The participants were also asked to consent for medical records review and this may have affected response rate as this has been previously shown to decrease response rate (Dunn et al., 2004). The medical records review did provide valuable information with regards to opioid dose and meant that only two women were unable to be categorised into an opioid category following its use compared to 11 women prior to this.

A further limitation of the studies was that mental health was unable to take into account during either Cox regression (cohort study) or multiple logistic regression (cross-sectional study). The cohort study did not include depression or anxiety as a possible confounders (as this data was not available for the cohort), and this is a limitation as mental health has been shown to be closely interlinked with pain, opioid use and sexual function (Gracia et al., 2004; Gureje et al., 1998; Scherrer et al., 2014). In retrospect, it would have been helpful to have included depression and anxiety within analysis of the cohort study, and this would have been particularly useful in relation to the low libido outcome (however due to low rates of low libido this would not have altered the results significantly). The cross-sectional study did include items to assess mental health, unfortunately due to the low response rate, there was insufficient statistical power to undertake multiple logistic regression.

Another potential limitation is how representative the sampling frames (GP practices contributing to CPRD and actively involved in research) are of the wider UK population. Practices that contribute to CPRD and participate in research have self-selected from a wider pool of practices. Previous work set in the West Midlands has shown that active research practices are from more deprived areas, more likely to undertake postgraduate GP training, have larger practice areas (and patient lists) and achieve higher QoF points (explained in section 4.6.1). However, despite these differences being statistically significant, the absolute difference was small, and these differences were felt to be unlikely to have an impact clinically (Mcmanus et al., 2008). A further study in the Trent region found similar results but also added that there was no difference in standardised mortality ratios (Hammersley et al., 2002). It is likely, therefore, that the practices included in the cross-sectional study are

representative of the general population and the results are generalisable to other GP practices within the UK. CPRD has also been shown to be representative of the UK population when compared with census data, however there is some concern that the participating practices may be high achieving when compared with other practices (Campbell et al., 2013; Herrett et al., 2010). Despite these differences, it is likely that both CPRD and the practices included in the cross-sectional research were representative of GP's within England which therefore improves the external validity of the results through avoiding systematic differences between the study population and the population of interest.

Overall considering the strengths and limitations of the thesis as discussed above, the results are likely to be generalisable to primary care in the UK (and other populations with similar healthcare systems for accessing opioids), however the low response rate to the cross-sectional study has decreased the confidence with which a conclusion for FSD can be drawn.

11.3 Implications for clinical practice and research

The comparison between the results for sexual dysfunction in the systematic review, other research examining sexual issues, the cross-sectional study and the cohort study suggest that CPRD is not the most appropriate way to research FSD. This is important for future research, as other methods of investigating this area should be considered, or if database research is undertaken then thought should be given to including data from free text within the records as well as Read Codes. However the postal survey was subject to a poor response rate, so potentially future research

might be embedded within larger studies, such that participants have already been recruited for the study and the focus is not purely on sexual problems.

Future research should continue to use definitions of long-term opioids and opioid dose stratification as exemplified in this thesis and previous research (Dunn et al., 2010; Von Korff et al., 2008; Saunders et al., 2009). In this way it will ensure that future examination of this area is comparable, particularly when the same adverse effect is being investigated using different methods. Recent guidelines suggest that there is a research gap in those using opioids for six months or longer, and therefore this research could be reproduced to reflect this duration of opioid use (British Medical Association, 2017). The cross-sectional study investigated daily opioid dose and how this was related to adverse effects. There appeared to be a dose response with increasing doses of opioids associated with increasing odds of FSD (not statistically significant, except in the sensitivity analysis). The results from this thesis appear to show that both duration of opioid use and dose are related to adverse effects, and if possible, then both of these should be taken into account in the design of future studies.

This research did not investigate specific opioid type. There is a need to investigate if there are any specific opioids that are associated with a higher risk of adverse effects, independent of daily morphine equivalent dose, as previous work appears to have shown different safety profiles when comparing specific opioids (Solomon et al., 2010a). The mode of delivery of opioid (oral vs. transdermal) would benefit from further research to investigate whether this modifies the risk of adverse effects. This could be investigated this within the thesis, as the cross-sectional study had

insufficient numbers of women reporting the use of transdermal opioids, and information on individual opioid type was not available in the cohort study.

There is also an under investigated area relating to the persistence of adverse effects after stopping regular opioid use. The cohort study did not allow participants to move between exposure groups, so determining if the effect disappears once opioids are stopped is an area that warrants further investigation. The cross-sectional study, by its very nature, only investigated a single period in time. This could be achieved by using patients as their own controls (case–crossover control study) and re-analysing if the participants become a non-opioid user, however this would be difficult to do within a database as symptoms are not often marked as resolved within primary care systems.

A further implication for research is the potential effect that opioids might have on oestrogen levels through disruption of the HPG axis (symptoms of menopause and amenorrhoea). Oestrogen has been identified as a key modulator of pain in humans (Craft, 2007; Hassan et al., 2014; Paller et al., 2009). In post-menopausal women, HRT has been associated with improvement in some types of pain and worsening in some specific conditions such as migraines (Aloisi and Bonifazi, 2006; Craft, 2007). This is a complex relationship, but if opioids have an effect in increasing menopausal symptoms and amenorrhoea (both low oestrogen states), could this then have a further effect on pain. Further hormonal assay studies in women, pre and post long-term opioid therapy might add further evidence to the part played by HPG hormones to determine if there is an absolute difference and how this relates to changes in pain.

This thesis has highlighted the link between opioid use and reproductive and sexual dysfunction in women. It is important that this is considered by GP's when considering prescribing opioids in the short-term, and during review of prescribed long-term opioids. This thesis adds to the growing evidence for the burden of adverse effects associated with long-term opioids and highlights an area of adverse effects that are less well known (Bedson et al., 2019a; Dunn et al., 2010; Saunders et al., 2009). Guidelines currently suggest that prior to prescribing opioids, the full risks and benefits should be discussed with the patient, and this includes the risks of reproductive and sexual dysfunction (British Medical Association, 2017). The same guidance recommends that opioids should be reviewed soon after starting to assess effectiveness and for adverse effects and that regular monitoring should be undertaken. Guidance around opioid use in the UK now suggests avoiding using opioids if they are not necessary, avoiding escalating dose of opioids that are already in use and finally de-escalating those on long-term opioids to lower doses, all of this is important to prevent the increase that has been seen in opioid use over the past 20 years from increasing further (Bedson et al., 2016; British Medical Association, 2017; Foy et al., 2016). This means that introducing a discussion around sexual and reproductive health would be considered part of the process of initial and ongoing prescribing of opioids based on the current evidence. This should not create an extra burden on GP's as reviews of opioids should already be occurring regularly.

This thesis adds to the growing evidence for adverse effects associated with opioid use for CNCP, and this should be considered by clinicians when considering initiating opioids or increasing dose of opioids for CNCP, and when undertaking medicine reviews for continuation of use or considering dose de-escalation.

11.4 Conclusion

The overall aim of this thesis was to investigate sexual and reproductive dysfunction and whether this was associated with opioid use for CNCP. This thesis has investigated this question with three separate studies; a systematic review, a database cohort study and a cross-sectional survey. The thesis identified this as an area with limited relevant research and then investigated this further. The results from the cohort study support the hypothesis that opioid use is associated with reproductive dysfunction. The cross-sectional study added to this body of evidence indicating a relationship between increasing daily morphine equivalent opioid dose and FSD, however this was not statistically significant. The work from this thesis has increased the knowledge around sexual and reproductive dysfunction associated with opioid use in women of reproductive age, and should be used to further develop the discussion around risks and benefits of opioid use in CNCP, particularly musculoskeletal pain.

12 References

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Appendix 1 Systematic review protocol

Arthritis Research UK Primary Care Centre
Systematic Review Protocol & Support Template

This template is primarily intended to help you plan your review in a systematic way. A copy of this completed form will be available via the intranet to help others carrying out reviews in the future and to avoid duplicating work already undertaken in the Centre. Keeping a record of all the reviews will also assist in planning the work of the Centre and ensuring adequate methodological support. Not all the information will be relevant to every review. However, items can be adapted to fit the type of review that is being undertaken.

Please complete the form in as much detail as possible for your review and email to Jo Jordan, j.jordan@keele.ac.uk

Title of the review	The risk of adverse effects on endocrine function in female patients with chronic non-cancer pain (CNCP) prescribed long-term opioid analgesia.
First reviewer	Emily Wersocki
Team of reviewers	Emily Wersocki John Bedson Ying Chen Kate Dunn
Supervisor/Project PI	John Bedson
Clinical Portfolio Group	
Project title (if different from review title)	

Support – please state if advice/training or personnel required at each stage	
SR overview	Yes
Protocol development	Yes
Literature searching	Yes
Quality appraisal	No EW
Data Extraction	Support with data extraction and training.

Synthesis	No EW
Writing up	No EW

Background to review Brief introduction to the subject of the review, including rationale for undertaking the review and overall aim
With age, and particularly in females, there is an increased susceptibility to the chronic pain conditions for which treatment according to current guidelines may involve the use of opioids. Though much is known about the effects of using long-term opioids in males and the adverse consequences of so doing, there has been very little work relating to their effect on females. However this is an important area for clinicians and female long-term opioid users to understand better. Theoretically, opioids can interfere with the normal hormonal pathways in humans and therefore disrupt the normal function of hormones which regulate the menstrual cycle, the menopause and consequently fertility. This has previously been demonstrated in methadone users, although there are obvious demographic differences between this group and the general population that could potentially account for this. Consequently, if opioid analgesics have some form of adverse effect on fertility, and if this is combined with an aging population susceptible to MSK pain, that also may choose to have children later in life, the combined effect may be to limit a woman's choice to do so because of the analgesic she is prescribed. Determining if long-term opioid use is associated with menstrual disturbance and potentially fertility problems will help inform guidelines and prescribing that can be tailored to individual needs without compromising a patient's reproductive capacity.

2. Specific objectives
To review the literature around the endocrinological effects of taking long term opiates for CNCP in females.

3. a) Criteria for including studies in the review If the PICOS format does not fit the research question of interest, please split up the question into separate concepts and put one under each heading	
Population, or participants and conditions of interest	Female 18-55 years old. CNCP taking opioids (including neuropathic pain) Studies including men and women will be included if data is available separately for women. Papers with age ranges outside 18-55 will be included if stratified data is available for appropriate age groups. If the paper focuses on CNCP in a specific group this will be included if the control group is matched.
Interventions or exposures	Exposure: Long term opioid use (>1 month prescriptions for opioids) for chronic non-cancer pain. Each paper will be reviewed for how they define long term and included if this is >1month.
Comparisons or control groups	No control/comparison group required for inclusion but if study includes comparison group it will be included.
Outcomes of interest	Primary Outcome - Endocrinological side effects – premature menopause, infertility, fertility treatment, IVF treatment, irregular menstrual cycle, hypogonadism, libido.
Setting	Any
Study designs	Cohort studies RCTs Diagnostic studies, treatment based studies Case-control studies Case studies Case series Cross sectional studies

3. b) Criteria for excluding studies not covered in inclusion criteria Any specific populations excluded, date range, language, whether abstracts or full text available, etc

methadone users for rehabilitation from illegal drug use and no chronic pain usage illegal opiate use cancer pain palliative care non pain conditions e.g. opiates for breathlessness papers not in English where translations are not available non-human subjects full text unavailable systematic reviews editorials letters

4. Search methods	
Electronic databases Please list all databases that are to be searched and include the interface (eg NHS, EBSCO, etc) and date ranges searched for each	AMED, MEDLINE, PsychINFO, CINAHL Embase,Toxline Web of Science: Citation Index
Other methods used for identifying relevant research ie contacting experts and reference checking	Cochrane library - Reference checking from any systematic reviews found. Citation tracking. Contact any relevant experts in the area.
Journals hand searched If any are to be hand searched, please list which journals and date searched from, including a rationale.	No

5. Methods of review

Details of methods Number of reviewers, how agreements to be reached and disagreements dealt with, etc.	Selected databases to be searched with predefined criteria. Results to be downloaded onto RefWorks and duplicates excluded Titles screened and inclusion/exclusion criteria applied by EW Abstracts screened and inclusion/exclusion criteria applied by EW, YC and JB (EW and one other reviewer, third reviewer if disagreement) Assess full-text articles for eligibility by EW, YC and JB. (EW and one other reviewer, third reviewed if disagreement) Disagreements regarding inclusion to be settled by KD Papers to be included will be assessed for quality using CASP check lists. Data will be extracted using a standardised proforma.
Quality assessment Tools or checklists used with references or URLs	http://www.casp-uk.net/ CASP checklists appropriate for each study design.

Data extraction What information is to be collected on each included study. If databases or forms on Word or Excel are used and how this is recorded and by how many reviewers	Using Word proforma if <20 papers to be included are identified. First 3 papers the proforma will be completed by EW and JB to ensure reproducibility then EW will review the remaining papers independently. Author Title Year Journal/Source/Country Aim of study Study design type of study recruitment method non responders? Drop outs? Length of follow up? Measurement bias? Recall bias? Classification bias? Blinded? Population – number included in study, sampling method target population – age/sex setting Type of pain condition Baseline endocrine function Confounding factors? Any special characteristics of study population? Comparison Population comparison how were they selected? Matched groups? Intervention – Length of opioid use – How is long term opioid use defined? Route of administration Outcome – Endocrine side effects recorded (clinical, biochemical or both) Valid/reliable results? (using CASP checklist for quality of paper by EW) Statistically significant? Specific data extracted p values, confidence intervals.

Narrative synthesis Details of what and how synthesis will be done	Synthesis to be done by EW following review of the literature. It will most likely be thematic and discuss individual effects and the papers that discussed these effects.
Meta-analysis Details of what and how analysis and testing will be done. If no meta-analysis is to be conducted, please give reason.	Unlikely to yield data that can be inputted into a meta-analysis.
Grading evidence System used, if any, such as GRADE	Not applicable

6. Presentation of results	
Additional material Summary tables, flowcharts, etc, to be included in the final paper	Summary tables for papers included which show methods and results. Flowchart to show papers identified at each stage and how many were excluded (PRISMA flow diagram as the model for this)
Outputs from review Papers and target journals, conference presentations, reports, etc	Presentation at a conference. Potentially a publication dependent on findings.

7. Timeline for review – when do you aim to complete each stage of the review	
Protocol	16/10/14
Literature searching	9/11/14

Quality appraisal	20/12/14
Data extraction	20/12/14
Synthesis	23/01/14
Writing up	26/1/15

Please send your completed protocol to Jo Jordan (see email below) as we would like to put these on the Intranet.

The systematic review team are available to answer any queries or give advice on completing your review. Systematic review workshops are run at least once a year, or can be arranged on an ad hoc basis if needed by a group. Presentations from previous workshops can be found on the Centre's Intranet.

Jo Jordan – j.jordan@keele.ac.uk

Appendix 2: Systematic review data collection form

Reference number	
Author (year)	
Title	
Journal/source country	
Aim	
Study Design	
CASP checklist: Are the results of the trial valid?	
Recruitment method	
Intervention group: size Sampling method Characteristics	
Control group: size sampling method characteristics matched sample?	
Target population (inc type of pain)	
Inclusion criteria	
Exclusion criteria	
Population characteristics at baseline Including baseline endocrine function	
Special characteristics of group in study	
Intervention - opiate type, route definition of chronic use	
Blinded?	
Setting	
Outcome measures used/measurement tools	
Validitiy/reliability of measures. Measurement, recall, classification bias?	

Outcomes – results and statistical significance (include p values/ confidence interval)	
Statistical techniques	
Implementation measures – non responders, drop outs, length of follow up	
Overall conclusion	
Further research questions	
Reviewers comments	

Appendix 3: Systematic review search strategies

Medline

Database: Ovid MEDLINE(R) <1946 to October Week 1 2014> on 14/10/14
Rerun database: NHS HDAS 2014-2016
Search Strategy:

		Ovid 1946 – October 2014	2014-2016
1	exp Analgesics, Opioid/	95669	5751
2	analgesic opioid.mp.	45	0
3	exp Narcotics/	103046	5903
4	narcotic.mp.	37290	0
5	exp Opiate Alkaloids/	77926	2936
6	opiate.mp.	18330	0
7	opioid.mp.	77340	0
8	narcotic analgesic agent.mp.	18	0
9	acemethadone.mp.	0	0
10	acetylmethadol.mp.	277	0
11	alfenta.mp.	3	0
12	Alfentanil/	1630	19
13	alfentanil.mp.	2240	0
14	amidone.mp.	28	0
15	anileridine.mp.	59	0
16	ardinex.mp.	0	0
17	exp Benzomorphans/	3369	27
18	benzomorphan*.mp.	967	0
19	Buprenorphine/	4003	398
20	buprenorphine.mp.	4859	0
21	buprenex.mp.	2	0
22	Butorphanol/	963	54
23	butorphanol.mp.	1252	0
24	carfentanil.mp.	208	0
25	exp Codeine/	5621	451
26	codeine.mp.	5679	0
27	codinovo.mp.	0	0
28	delsym.mp.	0	0
29	demerol.mp.	191	0
30	Dextromoramide/	252	0
31	dextromoramide.mp.	332	0
32	dezocine.mp.	77	0
33	diacetyl morphine.mp.	5	0
34	diamorphine.mp.	395	0

35 dicodid.mp.	5	0
36 dihydrocodeinone.mp.	35	0
37 dihydrocodeine.mp.	413	0
38 dihydroetorphine.mp.	69	0
39 dihydrohyroxycodeinone.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	0	0
40 Dihydromorphine/	218	0
41 dihydromorphine.mp.	412	0
42 dihydrone.mp.	12	0
43 dilaudid.mp.	61	0
44 dimepheptanol.mp.	0	0
45 dinarkon.mp.	0	0
46 dionine.mp.	24	0
47 Diprenorphine/	543	5
48 diprenorphine.mp.	760	0
49 dolantin.mp.	77	0
50 dolargan.mp.	2	0
51 dolcontral.mp.	7	0
52 dolophine.mp.	10	0
53 dolosal.mp.	21	0
54 dolsin.mp.	13	0
55 duragesic.mp.	35	0
56 duramorph.mp.	13	0
57 dyhydromorphinone.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	0	0
58 exp Dynorphins/	2890	82
59 dynorphin.mp.	3786	0
60 endomorphin.mp.	645	0
61 eseroline.mp.	46	0
62 Ethylketocyclazocine/	557	0
63 ethylketocyclazocine.mp.	803	0
64 eucodal.mp.	2	0
65 fenoperidine.mp.	0	0
66 exp Fentanyl/	13735	615
67 fentanyl.mp.	17353	0
68 fioricet.mp.	3	0
69 fortral.mp.	46	0

70 hycodan.mp.	3	0
71 hycon.mp.	4	0
72 Hydrocodone/	389	81
73 hydrocodon*.mp.	659	0
74 hydrocon.mp.	0	0
75 Hydromorphone/	1056	61
76 hydromorphon*.mp.	1484	0
77 hydroxycodeinon.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	0	0
78 isocodeine.mp.	5	0
79 isonipecain.mp.	0	0
80 isopromedol.mp.	5	0
81 kaolin-pectin.mp.	30	0
82 ketobemidone.mp.	159	0
83 laudacon.mp.	0	0
84 lealgin.mp.	0	0
85 Levallorphan/	339	0
86 levallorphan.mp.	483	0
87 levamethadyl.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	0	0
88 levodroman.mp.	0	0
89 levomethadryl.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	0	0
90 Levorphanol/	575	0
91 levorphan*.mp.	811	0
92 lexir.mp.	8	0
93 lidol.mp.	8	0
94 lorfan.mp.	18	0
95 lofentain.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease	0	0

supplementary concept word, unique identifier]		
96 lydol.mp.	4	0
97 exp Meperidine/	5512	61
98 meperidine.mp.	6309	0
99 Meptazinol/	184	0
100 meptazinol.mp.	219	0
101 methadol.mp.	65	0
102 exp Methadone/	11037	475
103 methadone.mp.	13377	0
104 Methadyl Acetate/	417	0
105 methadyl acetate.mp.	427	0
106 moradol.mp.	32	0
107 morphia.mp.	9	0
108 exp Morphine/	35395	1108
109 morphine.mp.	49071	0
110 exp Morphine Derivatives/	46054	1743
111 morphine derivatives.mp.	2059	0
112 Ms contin.mp.	73	0
113 methylnaloxone.mp.	140	0
114 Nalbuphine/	647	16
115 nalbuphine.mp.	864	0
116 naloxiphan.mp.	0	0
117 nocistatin.mp.	100	0
118 nubain.mp.	47	0
119 numorphan.mp.	11	0
120 omnopon.mp.	32	0
121 operidine.mp.	0	0
122 exp Opium/	1897	36
123 opium.mp.	2662	0
124 oramorph.mp.	17	0
125 oxycodein*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	0	0
126 Oxycodone/	1420	244
127 oxycodone.mp.	2066	0
128 oxycone.mp.	2	0
129 oxyconum.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word,	0	0

unique identifier]		
130 oxycontin.mp.	161	0
131 Oxymorphone/	414	29
132 oxymorph*.mp.	616	0
133 pancodiene.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	0	0
134 pantopon.mp.	9	0
135 papaveretum.mp.	137	0
136 paracymethadol.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	0	0
137 paramorfan.mp.	0	0
138 paramorphan.mp.	0	0
139 paregoric.mp.	53	0
140 Pentazocine/	2264	25
141 pentazocine.mp.	2938	0
142 percocet.mp.	40	0
143 pethidine.mp.	2095	0
144 phenadone.mp.	2	0
145 Phenazocine/	485	1
146 phenazocine.mp.	528	0
147 phenbenzorphan.mp.	0	0
148 phenethylazocine.mp.	0	0
149 Phenoperidine/	214	0
150 phenoperidine.mp.	265	0
151 physeptone.mp.	3	0
152 Promedol/	113	3
153 promedol.mp.	245	0
154 propoxyphene.mp.	925	0
155 proptopine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	0	0
156 pyrrolamidol.mp.	17	0
157 rapifen.mp.	15	0
158 remifentanil.mp.	3198	0

159	revivon.mp.	13	0
160	robidone.mp.	0	0
161	stadol.mp.	43	0
162	Sufentanil/	1584	82
163	sufentanil.mp.	2207	0
164	sufentanyl.mp.	47	0
165	talwin.mp.	57	0
166	tamgesic.mp.	1	13
167	Thebaine/	328	0
168	thebaine.mp.	455	0
169	theocodin.mp.	0	0
170	Tilidine/	138	2
171	tilidine.mp.	170	0
172	Tramadol/	2265	275
173	tramadol.mp.	3074	0
174	trimeperidine.mp.	21	0
175	valoron.mp.	47	0
176	valerone.mp.	0	0
177	vicodin.mp.	40	0
178	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176	185980	128357

or 177		
179 exp Hypogonadism/		576
180 hypogonadism.mp.		0
181 endocrin*.mp.		0
182 exp Menstruation Disturbances/		655
183 menstrual disturbance.mp.		0
184 Amenorrhea/		147
185 amenorrhoea.mp.		0
186 Oligomenorrhea/		20
187 oligomenorrhoea.mp.		0
188 Menorrhagia/		149
189 menorrhagia.mp.		0
190 Metrorrhagia/		57
191 dysfunctional uterine bleeding.mp.		0
192 DUB.mp.		0
193 heavy menstrual bleed*.mp.		0
194 Polycystic Ovary Syndrome/		1011
195 polycystic ovary syndrome.mp.		0
196 PCOS.mp.		0
197 PCOD.mp.		0
198 Infertility, Female/		1272
199 Infertility, female.mp.		0
200 Primary Ovarian Insufficiency/		245
201 ovarian insufficiency.mp.		0
202 Anovulation/		61
203 anovulation.mp.		0
204 exp Reproductive Techniques, Assisted/		4131
205 assisted reproductive techniques.mp.		0
206 Libido/		192
207 libido.mp.		0
208 exp Sexual Dysfunction, Physiological/		1702
209 sexual dysfunction.mp.	11393	0
210 Menopause/	23851	879
211 menopause.mp.	35040	0
212 Menopause, Premature/	814	60
213 premature menopause.mp.	514	0
214 Climacteric/	4689	18
215 climacteric.mp.	6359	0
216 Perimenopause/	849	139
217 perimenopause.mp.	1379	0
218 metrorrhagia.mp.	2685	0
219 opioid induced endocrinopathy.mp.	2	0

220 opioid induced androgen deficiency.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7	0
221 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220	303896	175368
222 (ae or co or de).fs.	5108792	0
223 (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs).ti,ab.	806543	152685
224 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.	239759	20006
225 222 or 223 or 224	5589493	172691
226 178 and 221 and 225	1664	20

Re-run via NHS HDAS on 7/4/16

EMBASE

Database: Embase <1974 to 2014 Week 41> Searched on 13/10/14 Ovid Embase
Re-run via NHS HDAS 2014-2016 on 7/4/16
Search Strategy:

	13/10/14	Re run 7/4/16
1 opioid analgesic.mp.	1624	3203
2 exp narcotic analgesic agent/	252551	26857
3 narcotic analgesic agent.mp.	15398	2597
4 exp opiate/	52694	8210
5 opiate.mp.	105726	12734
6 narcotic*.mp.	39202	4445
7 opioid.mp. or opiate/	98099	14248
8 acemethadone.mp.	0	0
9 exp acetylmethadol/	442	4
10 acetylmethadol.mp.	574	5
11 alfenta.mp.	59	1
12 exp alfentanil(	6053	251

13	alfentanil.mp.	6231	258
14	amidone.mp.	19	2
15	exp anileridine/	135	1
16	anileridine.mp.	144	1
17	ardinex.mp.	3	0
18	exp benzomorphan derivative/	12092	316
19	exp benzomorphan/	88	2
20	benzomorphan*.mp.	1084	9
21	exp buprenorphine/	11466	1634
22	buprenorphine.mp.	12134	1869
23	buprenex.mp.	181	101
24	exp butorphanol/	2596	139
25	butorphanol.mp.	3114	173
26	exp carfentanil/	377	32
27	carfentanil.mp.	463	49
28	exp codeine/	17527	1255
29	exp codeine phosphate/	1070	94
30	codeine.mp.	19490	1481
31	codeine phosphate.mp.	1294	134
32	codinovo.mp.	2	0
33	delsym.mp.	35	2
34	demerol.mp.	1462	23
35	exp dextromoramide/	946	1
36	dextromoramide.mp.	959	2
37	exp dezocine/	213	34
38	dezocine.mp.	217	37
39	diacetyl morphine.mp.	12	0
40	exp diamorphine/	19181	1845
41	diamorphine.mp.	19248	1850
42	dicodid.mp.	64	1
43	dihydrocodeinone.mp.	47	1
44	exp dihydrocodeine/	2090	118
45	dihydrocodeine.mp.	2173	125
46	exp dihydroetorphine/	103	0
47	dihydroetorphine.mp.	117	0
48	dihydrohyroxycodeinone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
49	exp dihydromorphine/	675	11
50	dihydromorphine.mp.	1267	12
51	dihydrone.mp.	9	0
52	dilaudid.mp.	781	35
53	dimepheptanol.mp.	88	0
54	dinarkon.mp.	1	1

55 dionine.mp.	40	1
56 exp diprenorphine/	973	15
57 diprenorphine.mp.	1249	20
58 dolantin.mp.	634	2
59 dolargan.mp.	47	0
60 dolcontral.mp.	83	0
61 dolophine.mp.	278	6
62 dolosal.mp.	316	2
63 dolsin.mp.	39	0
64 duragesic.mp.	473	34
65 duramorph.mp.	128	7
66 dyhydromorphinone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
67 exp dynorphin/	5508	365
68 dynorphin.mp.	5691	387
69 endomorphin.mp.	848	101
70 exp eseroline/	58	2
71 eseroline.mp.	81	2
72 exp ethylketazocine/	1165	2
73 ethylketocyclazocine.mp.	555	1
74 eucodal.mp.	11	0
75 fenoperidine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
76 fentanyl/	46955	5198
77 fentanyl.mp.	50786	5494
78 fioricet.mp.	87	10
79 fortral.mp.	609	0
80 hycodan.mp.	98	2
81 hycon.mp.	7	1
82 hydrocodone/	3509	776
83 hydrocodon*.mp.	4576	962
84 hydrocon.mp.	0	0
85 hydromorphone/	6531	992
86 hydromorphon*.mp.	6706	1027
87 hydroxycodeinon.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1	0

88 isocodeine.mp.	12	0
89 isonipecain.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
90 isopromedol.mp.	4	0
91 kaolin-pectin.mp.	275	3
92 exp ketobemidone/	542	27
93 ketobemidone.mp.	567	28
94 laudacon.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
95 lealgin.mp.	6	0
96 exp levallorphan/	1012	1
97 levamethadyl.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
98 levodroman.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
99 levomethadryl.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
100 levorphanol/	2196	28
101 levorphan*.mp.	2291	33
102 lexir.mp.	18	0
103 lidol.mp.	10	0
104 lorfan.mp.	139	0
105 lofentain.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
106 lydol.mp.	14	0
107 meperidine.mp.	3331	174

108 meptazinol/	401	12
109 meptazinol.mp.	420	15
110 methadol.mp.	85	0
111 methadone/	25244	2325
112 methadone.mp.	27068	2595
113 methadyl acetate.mp.	30	0
114 moradol.mp.	32	0
115 morphia.mp.	26	2
116 morphine/	85227	6675
117 exp morphine derivative/	160505	14277
118 morphine.mp.	98239	7891
119 morphine derivative.mp.	1721	779
120 morphine sulfate/	6399	640
121 morphine sulfate.mp.	7391	764
122 MS contin.mp.	505	25
123 methynaloxone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
124 nalbuphine/	2653	134
125 nalbuphine.mp.	2712	140
126 naloxiphan.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
127 nocistatin/	108	8
128 nocistatin.mp.	118	8
129 nubain.mp.	439	5
130 numorphan.mp.	175	2
131 omnopon.mp.	128	0
132 operidine.mp.	8	0
133 opium.mp.	2338	221
134 oramorph.mp.	226	27
135 oxycodeine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
136 oxycodone/	10813	2073
137 oxycone.mp.	2	0
138 oxyconum.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title,	0	0

device manufacturer, drug manufacturer, device trade name, keyword]		
139 oxycontin.mp.	1100	162
140 oxymorphone/	1640	232
141 oxymorph*.mp.	1840	248
142 pancodiene.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
143 pantopon.mp.	76	0
144 papaveretum.mp.	169	1
145 paracymethadol.mp.	2	0
146 paramorfan.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
147 paramorphan.mp.	0	0
148 paregoric/	213	3
149 paregoric.mp.	234	3
150 pentazocine/	8456	295
151 pentazocine.mp.	8709	316
152 percocet/	688	57
153 percocet.mp.	704	71
154 pethidine/	21308	835
155 pethidine.mp.	21646	858
156 phenadone.mp.	4	2
157 phenazocine/	272	0
158 phenazocine.mp.	281	1
159 phenbenzorphan.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
160 phenethylazocine.mp.	0	0
161 phenoperidine/	689	2
162 phenoperidine.mp.	723	1
163 physeptone.mp.	56	1
164 promedol.mp.	182	7
165 propoxyphene.mp.	1045	39
166 protopine/	372	48
167 protopine.mp.	437	57
168 pyrrolamidol.mp. [mp=title,	0	0

abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]		
169 rapifen.mp.	255	7
170 remifentanil/	8500	1713
171 remifentanil.mp.	8714	1795
172 revivon.mp.	47	0
173 robidone.mp.	1	0
174 stadol.mp.	376	6
175 sufentanil/	7034	657
176 sufentanil.mp.	7387	681
177 sufentanyl.mp.	132	18
178 talwin.mp.	588	5
179 tamgesic.mp.	8	1
180 thebaine/	768	30
181 thebaine.mp.	884	36
182 theocodin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0
183 tilidine/	1033	32
184 tilidine.mp.	1055	33
185 tramadol/	13442	2380
186 tramadol.mp.	13900	2527
187 trimeperidine/	255	10
188 trimeperidine.mp.	263	12
189 valoron.mp.	381	2
190 valerone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	1
191 vicodin.mp.	503	47
192 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73	324288	33722

or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191		
193 exp hypogonadism/	12006	1687
194 hypogonad*.mp.	18699	2659
195 endocrin*.mp.	355449	26591
196 exp menstruation disorder/	52077	5808
197 menstruation disorder.mp.	8078	851
198 amenorrhea/	17264	1417
199 amenorrhoea.mp.	3290	242
200 oligomenorrhea/	2373	357
201 oligomenorrhoea.mp.	372	36
202 menorrhagia/	7055	1235
203 menorrhagia.mp.	7837	1318
204 metrorrhagia/	4133	428
205 metrorrhagia.mp.	4498	457
206 dysfunctional uterine bleeding.mp.	1082	74
207 DUB.mp.	812	248
208 ovary polycystic disease/	17737	2943
209 polycystic ovary syndrome.mp.	10216	2781
210 PCOS.mp.	9305	2373
211 PCOD.mp.	332	19
212 exp female infertility/	36282	3810
213 female infertility.mp.	25640	7817
214 anovulation/	4598	370
215 anovulation.mp.	5779	373
216 libido/	6629	504
217 libido disorder/	4529	601
218 libido.mp.	12554	1207

219 exp sexual dysfunction/	61883	8318
220 sexual dysfunction.mp.	26201	5197
221 exp infertility therapy/	79955	10991
222 infertility therapy.mp.	13300	3580
223 heavy menstrual bleed*.mp.	650	332
224 exp ovary insufficiency/	11028	1571
225 ovarian insufficiency.mp.	777	805
226 premature ovarian failure/	2411	675
227 premature ovarian failure.mp.	3506	830
228 menopause/	36779	4685
229 menopause.mp.	54806	6597
230 early menopause/	1638	345
231 early menopause.mp.	2164	1034
232 climacterium/	7106	828
233 climacteric.mp.	5174	358
234 perimenopause.mp.	1272	212
235 opioid induced androgen deficiency.mp.	14	12
236 opioid induced endocrinopathy.mp.	5	7
237 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236	626039	64884
238 (ae or to or po or co).fs.	3119108	107761
239 (safe or safety).ti,ab.	653763	152336
240 ((adverse or undesireable or harm* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab.	440752	104498
241 exp postmarketing surveillance/	24257	4921
242 exp drug surveillance program/	18434	4061
243 exp "phase 4 clinical trial (topic)"/	465	492
244 intoxication/	177023	4475
245 exp drug toxicity/	82044	8998
246 adverse drug reaction/	161341	12158
247 exp drug monitoring/	41949	4140
248 exp drug hypersensitivity/	49903	4250
249 (toxicity or complication* or noxious or tolerability).ti,ab.	1208746	220560
250 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or	4590574	493304

248 or 249		
251 192 and 237 and 250	4088	234

TOXLINE

Toxline 20/10/2014

'opioid analgesic or narcotic analgesic agent or opiate or opioid or narcotic* AND Hypogonadism or endocrine* of Menstruation Disturbances or Amenorrhea or Oligomenorrhea or Menorrhagia or Metrorrhagia or dysfunctional uterine bleeding or DUB or heavy menstrual bleed* of Polycystic Ovary Syndrome or PCOS or PCOD or Infertility,Female, or Primary Ovarian Insufficiency or Ovarian insufficiency of Anovulation or Reproductive Techniques, Assisted of Libido or Sexual Dysfunction or Menopause or Menopause, Premature or Climacteric of Perimenopause or opioid induced endocrinopathy or opioid induced androgen deficiency'

PsychINFO

Database: PsycINFO <1806 to October Week 2 2014> Searched 13/10/14 via NHS HDAS
Search Strategy:
---
1 exp opiates/ (18725)
2 exp narcotic agonists/ (1241)
3 opiates.mp. (11588)
4 narcotic agonist.mp. (16)
5 opioid.mp. (13571)
6 acemethadone.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
7 acetylmethadol.mp. (117)
8 alfenta.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
9 alfentanil.mp. (86)
10 amidone.mp. (2)
11 anileridine.mp. (5)
12 ardinex.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
13 benzomorphan.mp. (25)
14 buprenorphine.mp. (1772)
15 buprenex.mp. (3)
16 buprenex.mp. (3)
17 butorphanol.mp. (168)
18 carfentanil.mp. (48)
19 exp Codeine/ (164)
20 codeine.mp. (434)
21 codeine phosphate.mp. (13)
22 codinovo.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)

23 delsym.mp. (1)
24 demerol.mp. (9)
25 dextromoramide.mp. (12)
26 dezocine.mp. (16)
27 diacetyl morphine.mp. (1)
28 diamorphine.mp. (61)
29 dicodid.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (1)
30 dihydrocodeinone.mp. (1)
31 dihydrocodeine.mp. (36)
32 dihydroetorphine.mp. (4)
33 dihydroxycodeinone.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
34 dihydromorphine.mp. (19)
35 dihydrone.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
36 dilaudid.mp. (15)
37 dimepheptanol.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
38 dimepheptanol.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
39 dinarkon.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
40 dionine.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
41 diprenorphine.mp. (81)
42 dolantin.mp. (3)
43 dolargan.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
44 dolcontral.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
45 dolophine.mp. (4)
46 dolosal.mp. (2)
47 dolsin.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
48 duragesic.mp. (6)
49 duramoprh.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
50 dihydromorphinone.mp. (5)
51 exp Dynorphins/ (263)
52 dynorphin.mp. (594)
53 endomorphin.mp. (97)
54 eseroline.mp. (2)
55 ethylketazocine.mp. (24)
56 eucodal.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
57 fenoperidine.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
58 exp Fentanyl/ (366)

59 fentanyl.mp. (802)
60 fioricet.mp. (2)
61 fortral.mp. (2)
62 hycodan.mp. (1)
63 hycon.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
64 hydrocodone.mp. (121)
65 hydromorphone.mp. (226)
66 hydroxycodeinon.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
67 hydroxycodeinon.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
68 hydroxycodeinon.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
69 isonipecain.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
70 isonipecain.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
71 isonipecain.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
72 isopromedol.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
73 kaolin-pectin.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
74 ketobemidone.mp. (5)
75 laudacon.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
76 lealgin.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
77 levallorphan.mp. (50)
78 levamethadyl.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
79 levodroman.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
80 levomethadryl.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
81 levorphanol.mp. (105)
82 levorphan*.mp. (106)
83 lexir.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
84 lexir.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
85 lidol.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
86 lorfan.mp. (4)
87 lofetain.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
88 lydol.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)

89 exp Meperidine/ or meperidine.mp. (193)
90 mepatazinol.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
91 methadol.mp. (19)
92 exp Methadone/ (1474)
93 methadone.mp. (6203)
94 methadyl acetate.mp. (11)
95 moradol.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
96 morphia.mp. (10)
97 exp Morphine/ (6041)
98 morphine.mp. (9154)
99 morphine derivative.mp. (2)
100 morphine sulfate.mp. (432)
101 morphine sulphate.mp. (78)
102 MS contin.mp. (9)
103 methylnaloxone.mp. (3)
104 nalbuphine.mp. (141)
105 naloxiphan.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
106 nocistatin.mp. (10)
107 nubain.mp. (3)
108 numorphan.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
109 omnopon.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
110 operidine.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
111 opium.mp. (532)
112 oramorph.mp. (1)
113 oxycodeine.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
114 oxycodone.mp. (427)
115 oxycone.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
116 oxyconum.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
117 oxycontin.mp. (94)
118 oxymorphone.mp. (54)
119 pancodiene.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
120 pantopon.mp. (3)
121 papaveretum.mp. (2)
122 paracymethadol.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
123 paramorfan.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
124 paramorphan.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)

125 paregoric.mp. (7)
126 exp Pentazocine/ (46)
127 pentazocine.mp. (272)
128 percocet.mp. (13)
129 pethidine.mp. (75)
130 phenadone.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
131 phenoazocine.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
132 phenbenzorphan.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
133 phenethylazocine.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
134 phenoperidine.mp. (4)
135 physeptone.mp. (2)
136 promedol.mp. (16)
137 propoxyphene.mp. (84)
138 protopine.mp. (1)
139 pyrrolamidol.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
140 rapifen.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
141 remifentanil.mp. (130)
142 revivon.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
143 robidone.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
144 sufentanil.mp. (62)
145 sufentanyl.mp. (1)
146 talwin.mp. (15)
147 tamgesic.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
148 thebaine.mp. (14)
149 theocodin.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
150 tilidine.mp. (10)
151 exp Tramadol/ (193)
152 exp Tramadol/ (193)
153 tramadol.mp. (363)
154 trimeperidine.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
155 valoron.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
156 valerone.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (0)
157 vicodin.mp. (21)
158 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45

or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 (30909)
159 exp Hypogonadism/ (694)
160 hypogonadism.mp. (494)
161 hypogonad*.mp. (593)
162 endocrin*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (9596)
163 exp menstrual disorders/ (1040)
164 menstrual disorder.mp. (19)
165 exp Amenorrhea/ (234)
166 amenorrhoea.mp. (100)
167 oligomenorrhoea.mp. (4)
168 menorrhagia.mp. (71)
169 metrorrhagia.mp. (3)
170 dysfunctional uterine bleeding.mp. (19)
171 DUB.mp. (88)
172 polycystic ovary syndrome.mp. (176)
173 exp endocrine sexual disorders/ (941)
174 PCOS.mp. (163)
175 PCOD.mp. (6)
176 infertility/ (1614)
177 female infertility.mp. (49)
178 anovulation.mp. (54)
179 libido/ (573)
180 libido.mp. (2637)
181 female sexual dysfunction/ (561)
182 sexual dysfunction.mp. (4500)
183 reproductive technology/ (1343)
184 infertility therapy.mp. (1)
185 premature ovarian failure.mp. (25)
186 ovarian insufficiency.mp. (15)
187 exp Menopause/ (2961)
188 menopause.mp. (3971)
189 early menopause.mp. (44)
190 early menopause.mp. (44)
191 climacterium.mp. (45)
192 climacteric.mp. (449)
193 perimenopause.mp. (222)
194 opioid induced androgen deficiency.mp. (3)
195 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or

182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 (24711)
196 exp "side effects (drug)"/ (44471)
197 exp toxicity/ (5002)
198 side effects.mp. (38696)
199 toxicity.mp. (7402)
200 (safe or safetly).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (21175)
201 adverse drug reaction.mp. (191)
202 ((adverse or undesireable or harm* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (31416)
203 drug monitoring.mp. (396)
204 drug hypersensitivity.mp. (12)
205 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 (111958)
206 158 and 195 and 205 (59)
207 158 and 195 (270)

CINAHL

Searched 13/10/14 CINHAL via HDAS.

Search history:
1. CINAHL; exp ANALGESICS, OPIOID/; 13832 results
2. CINAHL; exp NARCOTICS/; 16813 results
3. CINAHL; narcotics.ti,ab; 647 results
4. CINAHL; opiate.ti,ab; 1195 results
5. CINAHL; opioid.ti,ab; 5881 results
6. CINAHL; acemethadone.ti,ab; 0 results
7. CINAHL; acetylmethadol.ti,ab; 10 results
8. CINAHL; exp ALFENTANIL/; 200 results
9. CINAHL; alfenta.ti,ab; 1 results
10. CINAHL; alfentanil.ti,ab; 161 results
11. CINAHL; amidone.ti,ab; 0 results
12. CINAHL; anileridine.ti,ab; 1 results
13. CINAHL; ardinex.ti,ab; 0 results
14. CINAHL; benzomorphan.ti,ab; 1 results
15. CINAHL; buprenorphine.ti,ab; 903 results
16. CINAHL; exp BUPRENORPHINE/; 1072 results
17. CINAHL; buprenex.ti,ab; 1 results
18. CINAHL; exp BUTORPHANOL/; 44 results
19. CINAHL; butorphanol.ti,ab; 38 results
20. CINAHL; carfentanil.ti,ab; 2 results
21. CINAHL; exp CODEINE/; 1096 results
22. CINAHL; codeine.ti,ab; 346 results
23. CINAHL; (codeine AND phosphate).ti,ab; 25 results
24. CINAHL; codinovo.ti,ab; 0 results
25. CINAHL; delsym.ti,ab; 0 results

26. CINAHL; demerol.ti,ab; 23 results
27. CINAHL; dextromoramide.ti,ab; 1 results
28. CINAHL; dezocine.ti,ab; 2 results
29. CINAHL; (diacetyl AND morphine).ti,ab; 0 results
30. CINAHL; diamorphine.ti,ab; 126 results
31. CINAHL; dicodid.ti,ab; 0 results
32. CINAHL; dihydrocodeinone.ti,ab; 1 results
33. CINAHL; dihydrocodeine.ti,ab; 21 results
34. CINAHL; dihydroetorphine.ti,ab; 0 results
35. CINAHL; dihydrohyroxycodeinone.ti,ab; 0 results
36. CINAHL; dihydromorphine.ti,ab; 0 results
37. CINAHL; dihydrone.ti,ab; 0 results
38. CINAHL; dihydrone.ti,ab; 0 results
39. CINAHL; dilaudid.ti,ab; 15 results
40. CINAHL; dimepheptanol.ti,ab; 0 results
41. CINAHL; dinarkon.ti,ab; 0 results
42. CINAHL; dionine.ti,ab; 0 results
43. CINAHL; diprenorphine.ti,ab; 6 results
44. CINAHL; dolantin.ti,ab; 1 results
45. CINAHL; dolargan.ti,ab; 0 results
46. CINAHL; dolcontral.ti,ab; 0 results
47. CINAHL; dolophine.ti,ab; 4 results
48. CINAHL; dolosal.ti,ab; 0 results
49. CINAHL; dolsin.ti,ab; 0 results
50. CINAHL; duragesic.ti,ab; 16 results
51. CINAHL; duramoprh.ti,ab; 0 results
52. CINAHL; dyhydromorphinone.ti,ab; 0 results
53. CINAHL; dynorphin.ti,ab; 28 results
54. CINAHL; endomorphin.ti,ab; 6 results
55. CINAHL; eseroline.ti,ab; 0 results
56. CINAHL; ethylketazocine.ti,ab; 0 results
57. CINAHL; eucodal.ti,ab; 0 results
58. CINAHL; fenoperidine.ti,ab; 0 results
59. CINAHL; exp FENTANYL/; 2008 results
60. CINAHL; fentanyl.ti,ab; 1443 results
61. CINAHL; fioricet.ti,ab; 2 results
62. CINAHL; fortral.ti,ab; 0 results
63. CINAHL; hycodan.ti,ab; 0 results
64. CINAHL; hycon.ti,ab; 0 results
65. CINAHL; hydrocodone.ti,ab; 165 results
66. CINAHL; hydrocodon*.ti,ab; 165 results
67. CINAHL; hydrocon.ti,ab; 0 results
68. CINAHL; hydromorphone.ti,ab; 225 results
69. CINAHL; hydroxycodeinon.ti,ab; 0 results
70. CINAHL; isocodeine.ti,ab; 0 results
71. CINAHL; isonipecain.ti,ab; 0 results
72. CINAHL; isopromedol.ti,ab; 0 results
73. CINAHL; kaolin-pectin.ti,ab; 1 results
74. CINAHL; ketobemidone.ti,ab; 7 results

75. CINAHL; laudacon.ti,ab; 0 results
76. CINAHL; lealgin.ti,ab; 0 results
77. CINAHL; levallorphan.ti,ab; 0 results
78. CINAHL; levamethadyl.ti,ab; 0 results
79. CINAHL; levodroman.ti,ab; 0 results
80. CINAHL; levomethadryl.ti,ab; 0 results
81. CINAHL; levorphanol.ti,ab; 16 results
82. CINAHL; lexir.ti,ab; 0 results
83. CINAHL; lidol.ti,ab; 0 results
84. CINAHL; lorfan.ti,ab; 0 results
85. CINAHL; lofentain.ti,ab; 0 results
86. CINAHL; lydol.ti,ab; 0 results
87. CINAHL; exp MEPERIDINE/; 477 results
88. CINAHL; meperidine.ti,ab; 266 results
89. CINAHL; meptazinol.ti,ab; 11 results
90. CINAHL; methadol.ti,ab; 5 results
91. CINAHL; exp METHADONE/; 2256 results
92. CINAHL; methadone.ti,ab; 2075 results
93. CINAHL; (methadyl AND acetate).ti,ab; 0 results
94. CINAHL; moradol.ti,ab; 0 results
95. CINAHL; morphia.ti,ab; 2 results
96. CINAHL; exp MORPHINE/; 6888 results
97. CINAHL; morphine.ti,ab; 2726 results
98. CINAHL; (morphine AND derivative).ti,ab; 9 results
99. CINAHL; (morphine AND sulfate).ti,ab; 164 results
100. CINAHL; (morphine AND sulphate).ti,ab; 39 results
101. CINAHL; (MS AND Contin).ti,ab; 16 results
102. CINAHL; methynaloxone.ti,ab; 0 results
103. CINAHL; exp NALBUPHINE/; 58 results
104. CINAHL; nalbuphine.ti,ab; 64 results
105. CINAHL; naloxiphan.ti,ab; 0 results
106. CINAHL; nocistatin.ti,ab; 3 results
107. CINAHL; nubain.ti,ab; 1 results
108. CINAHL; numorphan.ti,ab; 0 results
109. CINAHL; omnopon.ti,ab; 1 results
110. CINAHL; operidine.ti,ab; 0 results
111. CINAHL; opium.ti,ab; 152 results
112. CINAHL; exp OPIUM/; 7047 results
113. CINAHL; oramorph.ti,ab; 6 results
114. CINAHL; oxycodeine.ti,ab; 0 results
115. CINAHL; exp OXYCODONE/; 679 results
116. CINAHL; oxycodone.ti,ab; 466 results
117. CINAHL; oxycone.ti,ab; 0 results
118. CINAHL; oxyconum.ti,ab; 0 results
119. CINAHL; oxycontin.ti,ab; 121 results
120. CINAHL; oxymorphone.ti,ab; 54 results
121. CINAHL; pancodiene.ti,ab; 0 results
122. CINAHL; pantopon.ti,ab; 0 results
123. CINAHL; papaveretum.ti,ab; 17 results

124. CINAHL; paracymethadol.ti,ab; 0 results
125. CINAHL; paramorfan.ti,ab; 0 results
126. CINAHL; paramorphan.ti,ab; 0 results
127. CINAHL; paregoric.ti,ab; 7 results
128. CINAHL; exp PENTAZOCINE/; 28 results
129. CINAHL; pentazocine.ti,ab; 43 results
130. CINAHL; percocet.ti,ab; 16 results
131. CINAHL; pethidine.ti,ab; 142 results
132. CINAHL; phenadone.ti,ab; 0 results
133. CINAHL; phenazocine.ti,ab; 0 results
134. CINAHL; phenbenzorphan.ti,ab; 0 results
135. CINAHL; phenethylazocine.ti,ab; 0 results
136. CINAHL; phenoperidine.ti,ab; 4 results
137. CINAHL; physeptone.ti,ab; 1 results
138. CINAHL; promedol.ti,ab; 0 results
139. CINAHL; exp PROPOXYPHENE/; 98 results
140. CINAHL; propoxyphene.ti,ab; 68 results
141. CINAHL; protopine.ti,ab; 8 results
142. CINAHL; pyrrolamidol.ti,ab; 0 results
143. CINAHL; rapifen.ti,ab; 0 results
144. CINAHL; remifentanil.ti,ab; 354 results
145. CINAHL; revivon.ti,ab; 0 results
146. CINAHL; robidone.ti,ab; 0 results
147. CINAHL; stadol.ti,ab; 14 results
148. CINAHL; exp SUFENTANIL/; 165 results
149. CINAHL; sufentanil.ti,ab; 169 results
150. CINAHL; sufentanyl.ti,ab; 5 results
151. CINAHL; talwin.ti,ab; 5 results
152. CINAHL; tamgesic.ti,ab; 0 results
153. CINAHL; thebaine.ti,ab; 3 results
154. CINAHL; theocodin.ti,ab; 0 results
155. CINAHL; tilidine.ti,ab; 5 results
156. CINAHL; exp TRAMADOL/; 424 results
157. CINAHL; tramadol.ti,ab; 418 results
158. CINAHL; trimeperidine.ti,ab; 0 results
159. CINAHL; valoron.ti,ab; 0 results
160. CINAHL; valerone.ti,ab; 0 results
161. CINAHL; vicodin.ti,ab; 15 results
162. CINAHL; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105 OR 106 OR 107 OR 108 OR 109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115 OR 116 OR 117 OR 118 OR 119 OR 120 OR 121 OR 122 OR 123 OR 124 OR 125 OR 126 OR

127 OR 128 OR 129 OR 130 OR 131 OR 132 OR 133 OR 134 OR 135 OR 136 OR 137 OR 138 OR 139 OR 140 OR 141 OR 142 OR 143 OR 144 OR 145 OR 146 OR 147 OR 148 OR 149 OR 150 OR 151 OR 152 OR 153 OR 154 OR 155 OR 156 OR 157 OR 158 OR 159 OR 160 OR 161; 24482 results
163. CINAHL; exp HYPOGONADISM/; 525 results
164. CINAHL; hypogonadism.ti,ab; 342 results
165. CINAHL; endocrin*.ti,ab; 4183 results
166. CINAHL; exp MENSTRUATION DISORDERS/; 3493 results
167. CINAHL; (menstruation AND disorder).ti,ab; 41 results
168. CINAHL; amenorrhoea.ti,ab; 118 results
169. CINAHL; oligomenorrhoea.ti,ab; 10 results
170. CINAHL; exp MENORRHAGIA/; 551 results
171. CINAHL; menorrhagia.ti,ab; 265 results
172. CINAHL; exp METRORRHAGIA/; 143 results
173. CINAHL; metrorrhagia.ti,ab; 22 results
174. CINAHL; (dysfunctional AND uterine AND bleeding).ti,ab; 84 results
175. CINAHL; DUB.ti,ab; 22 results
176. CINAHL; exp POLYCYSTIC OVARY SYNDROME/; 1020 results
177. CINAHL; (polycystic AND ovary AND syndrome).ti,ab; 623 results
178. CINAHL; PCOS.ti,ab; 396 results
179. CINAHL; PCOD.ti,ab; 9 results
180. CINAHL; (female AND infertility).ti,ab; 238 results
181. CINAHL; exp ANOVULATION/; 136 results
182. CINAHL; anovulation.ti,ab; 106 results
183. CINAHL; libido.ti,ab; 323 results
184. CINAHL; exp SEXUAL DYSFUNCTION, FEMALE/; 1787 results
185. CINAHL; (sexual AND dysfunction).ti,ab; 1509 results
186. CINAHL; (infertility AND therapy).ti,ab; 157 results
187. CINAHL; (heavy AND menstrual AND bleed).ti,ab; 1 results
188. CINAHL; (ovarian AND insufficiency).ti,ab; 41 results
189. CINAHL; (premature AND ovarian AND failure).ti,ab; 122 results
190. CINAHL; exp MENOPAUSE/; 9676 results
191. CINAHL; menopause.ti,ab; 3818 results
192. CINAHL; exp MENOPAUSE, PREMATURE/; 168 results
193. CINAHL; (premature AND menopause).ti,ab; 110 results
194. CINAHL; exp CLIMACTERIC/; 10741 results
195. CINAHL; climacteric.ti,ab; 260 results
196. CINAHL; exp PERIMENOPAUSE/; 181 results
197. CINAHL; perimenopause.ti,ab; 253 results
198. CINAHL; (opioid AND induced AND androgen AND deficiency).ti,ab; 6 results
199. CINAHL; (opioid AND induced AND endocrinopathy).ti,ab; 2 results
200. CINAHL; 163 OR 164 OR 165 OR 166 OR 167 OR 168 OR 169 OR 170 OR 171 OR 172 OR 173 OR 174 OR 175 OR 176 OR 177 OR 178 OR 179 OR 180 OR 181 OR 182 OR 183 OR 184 OR 185 OR 186 OR 187 OR 188 OR 189 OR 190 OR 191 OR 192 OR 193 OR 194 OR 195 OR 196 OR 197 OR 198 OR 199; 23697 results
201. CINAHL; 162 AND 200; 110 results

AMED

Database: AMED (Allied and Complementary Medicine) <1985 to October 2014>
Searched 13/10/14
Search Strategy:
---

1 exp analgesics opioid/ (230)
2 exp Narcotics/ (176)
3 opioids.mp. (570)
4 opiate.mp. (79)
5 alfentanil.mp. (13)
6 Buprenorphine/ (14)
7 buprenorphine.mp. (39)
8 butorphanol.mp. (1)
9 Codeine/ (9)
10 codeine.mp. (52)
11 codeine phosphate.mp. (7)
12 diamorphine.mp. (18)
13 dihydrocodeine.mp. (5)
14 dilaudid.mp. (1)
15 dolantin.mp. (2)
16 duragesic.mp. (3)
17 Dihydromorphinone/ (6)
18 dihydromorphinone.mp. (10)
19 dynorphin.mp. (5)
20 endomorphin.mp. (1)
21 Fentanyl/ (41)
22 fentanyl.mp. (147)
23 hydrocodone.mp. (15)
24 hydromorphone.mp. (47)
25 ketobemidone.mp. (1)
26 levorphanol.mp. (4)
27 meperidine.mp. (18)
28 Methadone/ (52)
29 methadone.mp. (116)
30 morphia.mp. (0)
31 morphine/ (249)
32 morphine.mp. (617)
33 morphine derivative.mp. (0)
34 morphine sulfate.mp. (17)
35 morphine sulphate.mp. (14)
36 MS contin.mp. (4)
37 nalbuphine.mp. (5)
38 Opium/ (42)
39 opium.mp. (76)
40 oramorph.mp. (2)
41 oxycodone.mp. (51)
42 oxycontin.mp. (6)
43 oxymorphone.mp. (5)

44 paregoric.mp. (1)
45 pentazocine.mp. (8)
46 percocet.mp. (1)
47 pethidine.mp. (7)
48 propoxyphene.mp. (6)
49 protopine.mp. (14)
50 remifentanil.mp. (4)
51 thebaine.mp. (4)
52 tilidine.mp. (2)
53 tramadol.mp. (50)
54 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 (1576)
55 ovarian insufficiency.mp. (1)
56 premature ovarian failure.mp. (6)
57 hypogonadism.mp. (18)
58 gonadal disorders/ (14)
59 endocrin*.mp. (511)
60 endocrin*.mp. (511)
61 exp menstruation disorders/ (423)
62 Amenorrhea/ (34)
63 amenorrhoea.mp. (22)
64 menorrhagia.mp. (19)
65 metrorrhagia.mp. (10)
66 dysfunctional uterine bleeding.mp. (11)
67 Ovary polycystic disease.mp. (0)
68 polycystic ovary syndrome/ (9)
69 polycystic ovary syndrome.mp. (41)
70 PCOS.mp. (27)
71 PCOD.mp. (14)
72 exp infertility female/ (166)
73 female infertility.mp. (19)
74 anovulation.mp. (10)
75 libido.mp. (39)
76 exp sexual dysfunctions/ (193)
77 sexual dysfunction.mp. (106)
78 infertility therapy.mp. (0)
79 exp Menopause/ (520)
80 menopause.mp. (582)
81 early menopause.mp. (3)
82 exp climacteric/ (540)
83 climacteric.mp. (52)
84 perimenopause.mp. (11)
85 opioid induced endocrinopathy.mp. (1)
86 opioid induced androgen deficiency.mp. [mp=abstract, heading words, title] (0)
87 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 (2098)

88 54 and 87 (10)

Web of Science

Web of Science 20/10/2014

TOPIC: (“opioid analgesic” or “narcotic analgesic agent” or opiate or opioid or narcotic*) AND **TOPIC:** ((safe or safety or side effect* or undesireable effect” or treatment emergent or tolerability or toxicity or adrs) or (ae or co or de) or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))) AND **TOPIC:** (Hypogonadism or endocrine* or “Menstruation Disturbances” or Amenorrhea or Oligomenorrhea or Menorrhagia or Metrorrhagia or “dysfunction uterine bleeding” or “DUB” or “heavy menstrual bleed*” of “Polycystic Ovary Syndrome” or PCOS or PCOD or “Infertility, Female” or “Primary Ovarian Insufficiency” or “ovarian insufficiency” of Anovulation or “Reproductive Techniques, Assisted” of Libido or “Sexual Dysfunction” or Menopause or “Menopause, Premature” or Climacteric or Perimenopause of “opioid induced endocrinopathy or “opioid induced androgen deficiency”)

Appendix 4: Systematic review sensitivity analysis

	Opioid	Menstrual disturbance	Libido	Hormone
Age ≤ 45				
Finch et al., 2000 [17]	Intrathecal	71% amenorrhoea	100% opioid users affected	Low LH
Njee et al., 2004 [28]	Intrathecal	31% amenorrhoea	N/A	N/A
Kim et al., 2004 [28] (1 patient)	Intrathecal	N/A	N/A	Low DHEA termed androgen deficient by author
Mussig et al., 2007 [27]	Oral	Amenorrhoea with hydromorphone which resolved with conversion to tramadol (1/1)	N/A	Oestrodiol low, LH and FSH normal
Fraser et al., 2009 [18]	Oral	Oliogo/amenorrhoea 23% (3/13)	N/A	Hormones within normal range (LH, FSH, SHBG, oestrodiol, progesterone)
Reddy et al., 2010 [32]	Oral	Amenorrhoea (1/1)	N/A	Low LH and oestrodiol
Summary		Oligo/amenorrhoea in 23-71% with 2 case studies with amenorrhoea	100% low libido in one study	Low hormone levels in 4/5 and normal in 1/5
Age < 55				
Kim et al., 2004 [28] (1 patient)	Intrathecal	N/A	N/A	Low DHEA termed androgen deficient by author
Daniell, 2008 [16]	Oral	52% opioid users non-surgical amenorrhoea, 20% controls p <0.05	N/A	Statistically significantly lower TT, fT, oestrodiol and DHEAS in cases compared to controls
Rhodin et al., 2010 [33]	Oral	81% (13/16) cases and 0% (0/6) controls	N/A	Statistically significantly lower oestrodiol, FSH, LH, post GnRH stimulation LH and

				FSH in cases compared to controls
Summary		52-81% amenorrhoea		2 studies with statistically significantly lower hormone levels in cases compared to controls
Premenopausal				
Abs et al., 2000 [1]	Intrathecal	67% (14/21) amenorrhoeic 7/21 irregular menstruation Controls – normal menstrual cycle (3/3)	N/A	Low LH (42.9% (9/21) of opioid users and 0% controls) and FSH (23.8% (5/21) of opioid users and 0% of controls). Non-significant difference
Roberts et al., 2001 [34]	Intrathecal	47% amenorrhoea	Low libido 71% affected	N/A
Wong et al., 2011 [44]	Oral	N/A	61% of opioid users and 70% of controls p = 0.62	Statistically significantly lower TT in cases compared to controls in those with low libido
Aurilio et al., 2011 [3]	Transdermal	0% (0/8) amenorrhoea	N/A	No statistically significant change in hormone levels (LH, FSH, TT, fT)
Summary		Oral/Intrathecal 47-67% amenorrhoea Transdermal buprenorphine 0%	61-71% low libido	One statistically significant study, one showing lower levels in cases compared to controls. Transdermal buprenorphine no change in hormones.

Appendix 5: Screenshot of systematic review publication

Comprehensive Review

PAIN

Comprehensive systematic review of long-term opioids in women with chronic noncancer pain and associated reproductive dysfunction (hypothalamic–pituitary–gonadal axis disruption)

Emily Wersocki[a,*], John Bedson[a], Ying Chen[a], Linda LeResche[b], Kate M. Dunn[a]

Abstract

A comprehensive systematic literature review of reproductive side effects in women aged 18 to 55 years treated with opioids for 1 month or longer for chronic noncancer pain. A search of 7 databases including EMBASE and Medline was undertaken (October 2014 and a limited rerun April 2016). The search contained keywords for opioids (generic and specific drug names) and side effects (generic and specific reproductive). Titles were screened using predefined criteria by a single reviewer and abstracts and full texts by 2 independent reviewers. A total of 10,684 articles were identified and 12 full texts (cohort [n = 1], case–control [n = 4], cross-sectional [n = 4], case series [n = 1], and case report [n = 2] with a maximum of 41 cases in 1 article) were included covering 3 different modes of administration: oral (n = 6), intrathecal (n = 5), and transdermal (n = 1). Amenorrhoea occurred in 23% to 71% of those receiving oral or intrathecal opioids. Decreased libido was seen in 61% to 100%. Of the 10 studies that undertook hormonal assays, only 2 studies showed a statistically significant decrease in hormone levels. This review supports the view that there is a potential relationship between the use of long-term opioids in women and reproductive side effects. The evidence is however weak and the mode of administration, duration, type, and dose of opioid might influence associations. Although hormone levels were statistically significant in only 2 studies, women exhibited clinically important symptoms (decreased libido and altered menstrual cycle). Further investigation is required with larger cohorts and analysis of different delivery methods.

Keywords: Women, Opioids, Chronic non cancer pain, Hypothalamic–pituitary–gonadal axis, Hypogonadism

1. Introduction

Chronic noncancer pain (CNCP) has been defined as any painful condition lasting for 3 months or more and not associated with neoplastic disease (cancer).[12] CNCP affects many people across the globe; a World Health Organization (WHO) 15 centre study showed that 22% of those attending primary care suffered from persistent pain, and women were more commonly affected than men.[23] There are many approaches to care of CNCP, including self care, physical rehabilitation, psychological approaches, medications, surgical intervention, and alternative medicine. Patients often need a combination of these, and in CNCP an integrated multidisciplinary approach is commonly required.[46] In 12% to 13% of patients with CNCP, opioids are prescribed.[8]

Since the late 1980s, there has been a trend towards increased opioid prescribing for CNCP and a recent U.K. observational database study showed a 38% increase in opioid prescribing from 2002 to 2009, this is despite a Cochrane review showing only weak evidence for their effectiveness.[6,32] Another systematic review did not find any studies that compared opioid use with nonopioid therapy that lasted more than a year with the majority lasting less than 16 weeks.[14]

Adverse effects are common among people taking opioids, and 80% of patients will experience at least one, such as constipation, somnolence, nausea, vomiting, dizziness, itching, dependency, tolerance, addiction, and opioid-induced hyperalgesia.[5,22,26,44] Chronic prescription opioid use in men can lead to hypogonadotrophic hypogonadism and decreased levels of sex hormones, particularly testosterone, leading to reproductive and sexual dysfunction. This is known as opioid-induced androgen deficiency; it is increasing in prevalence due to greater recognition and some studies have found up to 92% of those men treated with opioids are affected.[1,2,7,16,27,42] In women, it is recognised that illegal dependent opioid use (for instance, heroin) can be associated with hypogonadism and reproductive dysfunction (low libido, sexual dysfunction, and amenorrhoea), with menstrual irregularities affecting over 50% of women using illegal opioids.[10,20,39,40] The picture is less clear in women with respect to any association with prescription opioid use. Therefore, in light of the fact that nonprescription opioids can cause symptoms of reproductive dysfunction consistent with hypothalamic–pituitary–gonadal axis disruption (hypogonadism) in women, and that there is good evidence of hypogonadism in some men taking long-term

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] *Research Institute for Primary Care & Health Sciences, Keele University, Keele, United Kingdom,* [b] *Department of Oral Medicine, University of Washington, Seattle, WA, USA*

**Corresponding author. Address: Research Institute for Primary Care & Health Sciences, David Weatherall Building, Keele University, Staffordshire ST5 5BG, Keele, United Kingdom. Tel.: 01782 734889; fax: 01782 734719. E-mail address: ewersocki@gmail.co.uk (E. Wersocki).*

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Appendix 6: CPRD study Read Code List for Outcomes and Confounders

Outcomes

Menstrual Cycle

Readterm	Read Code	Med Code	ICD-10
Secondary amenorrhoea	K5901	2086	N91.1
Amenorrhoea NOS	K590z	33769	N91.2
Scanty or infrequent menstruation	K591.	18527	N91.5
Hypomenorrhoea	K5910	15438	N91.5
Oligomenorrhoea	K5911	1153	N91.5
Secondary oligomenorrhoea	K5913	12100	N91.4
Scanty or infrequent menstruation NOS	K591z	25358	N91.5
Irregular menstrual cycle	K594.	1065	N92.6
Irregular menstrual cycle NOS	K594z	25355	N92.6
Other menstruation disorder NOS	K59yz	29803	N92.6
Menstruation disorder NOS	K59z.	27829	N92.6
Amenorrhoea	K590.11	757	N91.2
Infrequent Menstruation	K591.11	21729	N91.5
Other menstruation disorders	K59y.00	15000	N92.5
Absence of menstruation	K590.	9632	N91.2

Libido

Readterm	Read Code	Med Code	ICD-10
Psychosexual dysfunction	E227.00	15649	no code
Lack of libido	E227.11	6362	no code
Unspecified psychosexual dysfunction	E227000	23534	no code
Inhibited sexual desire	E2271	2259	no code
Psychsexual dysfunction NOS	E227z00	20133	no code
[X] Lack of libido	Eu52013	21122	F52.0
[X] Lack of or loss of sexual desire	Eu52000	28283	F52.0
[V]Problem with sexual function	ZV417	16060	F52.9

Infertility

Readterm	Read Code	Med Code	ICD-10
Infertility - female	K5B..	1808	N97.9
Female infertility of anovulatory origin	K5B0.	4977	N97.0
Primary anovulatory infertility	K5B00	52132	N97.0
Secondary anovulatory infertility	K5B01	50116	N97.0
Female infertility of anovulatory origin NOS	K5B0z	63421	N97.0
Female infertility of pituitary - hypothalamic origin	K5B1.	69884	E23.0
Primary pituitary - hypothalamic infertility	K5B10	94448	E23.0
Secondary pituitary - hypothalamic infertility	K5B11	99535	E23.0
Female infertility of pituitary - hypothalamic cause NOS	K5B1z	62084	E23.0
Other female infertility	K5By.	36458	N97.8
Primary infertility unspecified	K5By0	2014	N97.9
Secondary infertility unspecified	K5By1	1943	N97.9
Other female infertility NOS	K5Byz	53018	N97.9
Female infertility NOS	K5Bz.	30392	N97.9
Introduction of gamete into uterine cavity	7E0A.	45538	no code
Implantation of fertilised egg into uterus	7E0A0	6024	no code
Intracervical artificial insemination	7E0A1	11305	no code
Intrauterine artificial insemination	7E0A2	11428	no code
Intrauterine insemination with superovulation using partner sperm	7E0A3	91652	no code
Intrauterine insemination with superovulation using donor sperm	7E0A4	88271	no code
Intrauterine insemination without superovulation using donor sperm	7E0A6	89588	no code
Transfer of embryo to uterus	7E0A7	57381	no code
Intrauterine insemination without superovulation using partner sperm	7E0A5	no code	no code
Other specified introduction of gamete into uterine cavity	7E0Ay	no code	no code
Introduction of gamete into uterine cavity NOS	7E0Az	50360	no code
[V]Infertility management	ZV26.	9938	Z31
[V]Artificial insemination NOS	ZV261	33401	Z31.1
[V]Infertility investigation and testing	ZV262	26088	Z31.4
[V]Infertility general advice and counselling	ZV264	39295	Z31.6
[V]Artificial insemination from husband	ZV265	30597	Z31.1
[V]In vitro fertilization	ZV267	30046	Z31.2
[V]Other assisted fertilization methods	ZV268	8981	Z31.3

[V]Other specified infertility management	ZV26y	26150	Z31.8
[V]Unspecified infertility management	ZV26z	69751	Z31.9
Artificial insemination	8C81	28455	no code
Treatment for infertility	8C8..	1810	no code
Female infertility therapy	8C82.	33458	no code
IVF	8C84.11	10238	no code
Treatment for infertility NOS	8C8Z.	9983	no code
In-vitro fertilisation	8C8Z.11	1938	no code
In vitro fertilisation (IVF)	7M0h.	52626	no code
IVF with donor sperm	7M0h0	89966	no code
In vitro fertilisation with donor sperm	7M0h011	91910	no code
IVF with donor eggs	7M0h1	64063	no code
In vitro fertilisation with done eggs	7M0h111	94632	no code
IVF with intracytoplasmic sperm injection (ICSI)	7M0h2	57000	no code
In vitro fertilisation with intracytoplasmic sperm injection (ICSI)	7M0h211	86010	no code
IVF with intracytoplasmic sperm injection (ICSI) and donor egg	7M0h3	97981	no code
In vitro fertilisation with intracytoplasmic sperm injection (ICSI) and donor egg	7M0h311	97044	no code
IVF with surrogacy	7M0h5	89716	no code
In vitro fertilisation with surrogacy	7M0h511	91845	no code
Other specified in vitro fertilisation (IVF)	7M0hy	93810	no code
In vitro fertilisation (IVF) NOS	7M0hz00	90936	no code

Menopause

Readterm	Read Code	Med Code	ICD-10
Menopause	1512	4383	no code
Postmenopausal state	151K.	30590	no code
Ovarian dysfunction	C16..	6352	E28.9
Primary ovarian failure	C1630	31030	E28.3
Ovarian dysfunction NOS	C16z.	44854	E28.9
Other ovarian dysfunction	C16y.00	58028	E28.8
Other ovarian failure	C163.00	3686	E28.8
Ovarian hypogonadism	C163.11	23802	E28.8
Secondary ovarian failure	C1631	15992	E28.3
Premature Menopause NOS	C163111	2087	E28.3
Ovarian hypogonadism	C1633	22836	E28.3
Early menopause	C1634	94499	E28.8
Other specified other ovarian failure	C163y	40672	E28.8

Other ovarian failure NOS	C163z	15075	E28.8
[X]Other ovarian dysfunction	Cyu4B	100934	E28.8
Menopausal and postmenopausal disorders	K5A..	9171	N95
Postmenopausal disorders	K5A..11	17628	N95
Premenopausal menorrhagia	K5A0.	15022	N92.4
Climacteric menorrhagia	K5A0.11	20795	N92.4
Postmenopausal Bleeding	K5A1.00	1583	N95.0
Menopausal or female climacteric state	K5A2.	4043	N95.1
Menopausal flushing	K5A20	9547	N95.1
Hot Flushes - Menopausal	K5A2011	814	N95.1
Menopausal sleeplessness	K5A21	15283	N95.1
Menopausal headache	K5A22	18730	N95.1
Menopausal concentration lack	K5A23	25549	N95.1
Menopausal symptoms NOS	K5A2z	828	N95.1
Postmenopausal atrophic vaginitis	K5A3.00	707	N95.2
Senile (atrophic) vaginitis	K5A3.11	1944	N95.2
Atrophy of vagina	K5A3000	16960	N95.2
Perimenopausal atrophic vaginitis	K5A5.	30359	N95.2
Perimenopausal menorrhagia	K5A6.	93526	N92.4
Other menopausal and postmenopausal states	K5Ay.	28046	N95.8
Menopausal and postmenopausal disorder NOS	K5Az.	45409	N95.9

Confounders

Thyroid

Readterm	Read Code	Med Code	ICD-10
Disorders of thyroid gland	C0...	1882	E00-E07
Simple and unspecified goitre	C00..	20311	E04.9
Simple goitre	C000.	2518	E04.0
Goitre NOS	C00z.	7911	E04.9
Nontoxic nodular goitre	C01..	1348	E041-E049
Nontoxic uninodular goitre	C010.	26700	E04.1
Nontoxic multinodular goitre	C011.	11743	E04.2
Nontoxic nodular goitre NOS	C01z.	34491	E04.9
Thyroiditis	C05..	1346	E060-E069
Acute thyroiditis	C050.	4898	E06.0
Acute nonsuppurative thyroiditis	C0500	67972	E06.0
Acute suppurative thyroiditis	C0501	70773	E06.0
Acute thyroiditis NOS	C050z	42323	E06.0
Chronic lymphocytic thyroiditis	C052.	26833	E06.3
Chronic fibrous thyroiditis	C053.	70244	E06.5
Iatrogenic thyroiditis	C054.	61026	E06.4
Other and unspecified chronic	C05y.	65444	E06.9

thyroiditis			
Retrosternal thyroid goitre	C000.11	3655	E04.0
Thyroid enlargement	C00z.11	1881	E04.9
Substernal thyroid goitre	C000.12	60288	E04.0
Thyroiditis NOS	C05z.	20909	E06.9
Other disorders of thyroid	C06..	43871	E070-E079
Thyroid-binding globulin abnormality	C06y0	41014	E07.8
Thyroid disorder NOS	C06z.	35957	E07.9
[X]Disorders of thyroid gland	Cyu1.	65175	E00-E07
Iodine-deficiency-related diffuse (endemic) goitre	C0A3.	37518	E01.0
[X]Other specified nontoxic goitre	Cyu12	72610	E04.8
[X]Other specified disorders of thyroid	Cyu15	73096	E07.8
[X]Iodine-deficiency-related (endemic) goitre, unspecified	Cyu16	101555	E01.2
Iodine-deficiency-related multinodular (endemic) goitre	C0A4.00	44459	E01.1
De Quervain's thyroiditis	C051.11	21747	E06.1
Subacute thyroiditis	C051.	30799	E06.1
Chronic thyroiditis with transient thyrotoxicosis	C05y4	65907	E06.2
[X]Other chronic thyroiditis	Cyu14	95335	E06.5
Autoimmune thyroiditis	C052.11	3857	E06.3
Hashimoto disease	C052.12	3436	E06.3
Other specified thyroid disorder NOS	C06yz00	27996	E07.8
Iodine-deficiency-related diffuse (endemic) goitre NOS	C0AX.00	54511	E01.2
[X]Other iodine-deficiency related thyroid disorders and allied conditions	Cyu10	26833	E01.8

Hypothyroid

Readterm	Read Code	Med Code	ICD-10
Congenital hypothyroidism NOS	C03z.00	51481	E03.1
Acquired hypothyroidism	C04..	3290	E03.9
Postsurgical hypothyroidism	C040.	28852	E89.0
Other postablative hypothyroidism	C041.	50275	E89.0
Irradiation hypothyroidism	C0410	11322	E89.0
Postablative hypothyroidism NOS	C041z	51706	E89.0
Iodine hypothyroidism	C042.	34221	E01.8
Other iatrogenic hypothyroidism	C043.	25913	E03.2
Hypothyroidism resulting from para-aminosalicylic acid	C0430	15743	E03.2
Hypothyroidism resulting from	C0431	97090	E03.2

phenylbutazone			
Hypothyroidism resulting from resorcinol	C0432	94915	E03.2
Iatrogenic hypothyroidism NOS	C043z	38976	E03.2
Postinfectious hypothyroidism	C044.	50860	E03.3
Acquired atrophy of thyroid	C045.	46345	E03.4
Autoimmune myxoedema	C046.	31971	E03.8
Other acquired hypothyroidism	C04y.	24748	E03.8
Hypothyroidism NOS	C04z.	3941	E03.9
Myxoedema coma	C04z1	59702	E03.5
Myxoedema coma	C04..11	1619	E03.9
thyroid deficiency	C04..12	14704	E03.9
hypothyroidism	C04..13	273	E03.9
Post ablative hypothyroidism	C040.11	47521	E89.0
Subclinical hypothyroidism	C047.00	95830	no code
Pretibial myxoedema hypothyroid	C04z.11	20310	E03.9
thyroid insufficiency	C04z.12	23014	E03.9
hypothyroid goitre acquired	C04z.13	18282	E03.9
TSH - thyroid-stimulating hormone deficiency	C1343	11146	E23.0
[X]Other specified hypothyroidism	Cyu11	73107	E03.8
Subclinical iodine-deficiency-related hypothyroidism	C0A5.00	718	E02.X

Hyperthyroid

Readterm	Read Code	Med Code	ICD-10
Thyrotoxicosis	C02..	677	E05
Toxic diffuse goitre	C020.	23315	E05.0
Toxic diffuse goitre with no crisis	C0200	26702	E05.0
Toxic diffuse goitre with crisis	C0201	57011	E05.0
Thyroid-associated dermopathy	C0202	100476	E05.0
Toxic diffuse goitre NOS	C020z	49334	E05.0
Toxic uninodular goitre	C021.	53280	E05.1
Toxic uninodular goite with crisis	C0211	no code	E05.1
Toxic uninodular goitre with no crisis	C0210	26869	E05.1
Toxic uninodular goitre NOS	C021z	61498	E05.1
Toxic multinodular goitre	C022.	11426	E05.2
Toxic multinodular goitre with crisis	C0221	No code	E05.2
Toxic multinodular goitre with no crisis	C0220	46985	E05.2
Toxic multinodular goitre NOS	C022z	53981	E05.2
Toxic nodular goitre unspecified	C023.	15790	E05.2
Toxic nodular goitre unspecified with no crisis	C0230	68512	E05.2
Toxic nodular goitre unspecified with c	C0231	100004	E05.2

Toxic nodular goitre NOS	C023z	49361	E05.2
Thyrotoxicosis from ectopic thyroid nodule	C024.	49508	E05.3
Thyrotoxicosis from ectopic thyroid nodule with no crisis	C0240	64656	E05.3
Thyrotoxicosis from ectopic thyroid nodule NOS	C024z	56270	E05.3
Subclinical hyperthyroidism	C025.	106640	no code
Thyrotoxicosis of other specified origin with no crisis	C02y0	51273	E05.8
Thyrotoxicosis of other specified origin with crisis	C02y1	106532	E05.8
Thyrotoxicosis factitia	C02y2	64856	E05.4
Thyroid crisis	C02y3	19205	E05.5
Thyrotoxicosis of other specified origin NOS	C02yz	34220	E05.8
Thyrotoxicosis without mention of goitre or other cause with no crisis	C02z0	26701	E05.9
Thyrotoxicosis without mention of goitre or other cause with crisis	C02z1	3194	E05.9
Thyrotoxicosis NOS	C02zz	26699	E05.9
Thyrotoxicosis of other specified origin	C02y.00	43136	E05.8
Hyperthyroidism	C02..11	1472	E05
Toxic Goitre	C02.12	10760	E05
[X]Other thyrotoxicosis	Cyu13	72690	E05.8
Graves' disease	C020.12	5257	E05.0
Thyrotoxicosis from ectopic thyroid nodule with crisis	C0241	no code	E05.3

Pituitary disorders

Readterm	Read Code	Med Code	ICD-10
Hyperprolactinaemia	C1310	6732	E22.1
Panhypopituitarism	C132.	5026	E23.0
Idiopathic panhypopituitarism	C1320	48590	E23.0
Post-birth injury panhypopituitarism	C1321	101601	E23.0
Postinfarction panhypopituitarism	C1322	70695	E23.0
Postinfective panhypopituitarism	C1323	44873	E23.0
Other specified panhypopituitarism	C132y	67154	E23.0
Panhypopituitarism NOS	C132z	33653	E23.0
Isolated ACTH deficiency	C1344	41193	E23.0
Iatrogenic pituitary disorders	C137.	56983	E23.1
Post-hypophysectomy hypopituitarism	C1371	44881	E89.3
Post-radiotherapy hypopituitarism	C1372	44247	E89.3
Iatrogenic pituitary disorder NOS	C137z	34459	E89.3

Empty sella syndrome	C138.	10071	R93.0
Pituitary apoplexy	C13A.	105321	no code
Pituitary disorders NOS	C13z.	12449	E23.7
Hypopituitarism NOS	C132.11	8552	E23.0
Hypoprolactinaemia	C134011	16004	E23.0
ACTH deficiency	C134411	11147	E23.0
Other anterior pituitary disorder NOS	C134z00	15488	E23.0
Anterior pituitary hormone deficiency NEC	C134z11	43908	E23.0
Iatrogenic hypopituitarism	C137.11	50958	E23.1
Hormone-induced hypopituitarism	C137000	105672	E23.1

Adrenal disorders

Readterm	Read Code	Med Code	ICD-10
Disorders of adrenal glands	C15..	12876	E24-E27
Adrenogenital disorders	C152.	20085	E25
Congenital adrenogenital syndrome	C1520	29640	E25.0
Acquired adrenogenital syndrome	C1521	69916	E25.9
Defective synthesis of 21 hydroxylase	C1522	29852	E25.0
Defective synthesis of 11B hydroxylase	C1523	12762	E25.0
Defective synthesis of 3B hydroxysteroid dehydrogenase	C1524	61615	E25.0
Defective synthesis of 17-20 desmolase	C1525	71483	E25.0
Defective synthesis of 17 alpha hydroxylase	C1526	43371	E25.0
Other adrenogenital syndrome with salt loss	C1527	67273	E25.0
Other adrenogenital syndrome without mention of salt loss	C1528	69764	E25.0
Other specified adrenogenital disorder	C152y	69134	E25.8
Adrenogenital disorder NOS	C152z	57321	E25.9
Adrenal gland disorder NOS	C15z.	41542	E27.9
[X]Other and unspecified primary adrenocortical insufficiency	Cyu49	48120	E27.3

Hypothalmic disorders

Readterm	Read Code	Med Code	ICD-10
Hypogonadotropic hypogonadism	C139.	98210	no code
Hypothalamic dysfunction, not	C13X.	36881	no code

elsewhere classified

Obesity

Readterm	Read Code	Med Code	ICD-10
Obesity and other hyperalimentation	C38..	66406	no code
Obesity	C380.	430	E66.9
Obesity due to excess calories	C3800	38799	E66.0
Drug-induced obesity	C3801	49250	E66.1
Extreme obesity with alveolar hypoventilation	C3802	38059	E66.2
Morbid obesity	C3803	8854	E66.8
Central obesity	C3804	22695	E66.9
Generalised obesity	C3805	25968	E66.9
Adult-onset obesity	C3806	104129	no code
Lifelong obesity	C3807	104421	no code
Childhood obesity	C3808	106771	no code
Simple obesity NOS	C38z0	11401	E66.9
[X]Obesity and other hyperalimentation	Cyu7.	52782	E65-E68
[X]Other obesity	Cyu70	69757	E66.8

Low BMI

Readterm	Read Code	Med Code	ICD-10
[X]Malnutrition	Cyu5.	72615	E40-E46
[X]Eating disorders	Eu50.	6159	F50
[X]Anorexia nervosa	Eu500	30570	F50.0
[X]Atypical anorexia nervosa	Eu501	34929	F50.1
[X]Bulimia nervosa	Eu502	9581	F50.2
[X]Atypical bulimia nervosa	Eu503	33863	F50.3
[X]Eating disorder, unspecified	Eu50z	36946	F50.9
[X]Bulimia NOS	Eu50211	6583	F50.2

Structural Gynaecological disorders

Readterm	Read Code	Med Code	ICD-10
Ovarian dysfunction	C16..	6352	E28.9
Hyperoestrogenism	C160.	63226	E28.0
Other ovarian hyperfunction	C161.	70689	E28.8
Hypersecretion of ovarian androgen	C1610	27824	E28.1
Hypersecretion of ovarian progesterone	C1611	63795	E28.8

Other specified other ovarian hyperfunction	C161y	100812	E28.8
Other ovarian hyperfunction NOS	C161z	71737	E28.8
Postablative ovarian failure	C162.	73041	E89.4
Postsurgical ovarian failure	C1620	102275	E89.4
Postirradiation ovarian failure	C1621	50462	E89.4
Other iatrogenic postablative ovarian failure	C1622	93791	E89.4
Other ovarian dysfunction	C16y.	58028	E28.8
Ovarian dysfunction NOS	C16z.	44854	E28.9
Polycystic ovaries	C164.00	1466	E28.2
Suppression of menstruation	K59y1	12792	N94.8
Supression of ovulation	K59y2	17826	N94.8
Artificial menopause state	K5A4.	19954	N95.3
H/O: hysterectomy	1599	6231	no code
H/O: bilateral oophorectomy	159B.	25199	no code
Androgen resistance syndrome	C1z5.	52001	E34.5
Polycystic ovarian syndrome	C165.	11347	E28.2
Androgen insensitivity syndrome	C1z5.11	49161	E34.5

Opioid misuse

Readterm	Read Code	Med Code	ICD-10
uses heroin on top of substitution therapy	1TE..00	86041	no code
Does not use heroin on top of substitution therapy	1TF..	85953	no code
Heroin misuse	1V65.	96925	no code
Drug addictn therap-methadone	8B23.11	6111	no code
Drug addiction detoxification therapy - methadone	8B2N.00	28976	no code
Drug addiction maintenance therapy - methadone	8B2P.00	30694	no code
Drug addiction maintenance therapy - buprenorphine	8B2Q.00	43487	no code
Drug addiction detoxification therapy - buprenorphine	8B2R.00	51052	no code
Opioid type drug dependence	E240.	16243	no code
Heroin dependence	E240.11	689	no code
Methadone dependence	E240.12	16374	no code
Morphine dependence	E240.13	22059	no code
Opium dependence	E240.14	32804	no code
Unspecified opioid dependence	E240000	38034	no code
Continuous opioid dependence	E2401	43075	no code
Episodic opioid dependence	E2402	20962	no code

Opioid dependences in remission	E2403	27960	no code
Opioid drug dependence NOS	E240z	24441	no code
Combined opioid with other drug dependence	E248.	26061	no code
Combined opioid with other drug dependence, unspecified	E2480	56194	no code
Combined opioid with other drug dependence, continuous	E2481	64265	no code
Combined opioid with other drug dependence, episodic	E2482	64277	no code
Combined opioid with other drug dependence NOS	E248z	73737	no code
Nondependent opioid abuse	E255.	26831	no code
Nondependent opioid abuse, unspecified	E2550	40536	no code
Nondependent opioid abuse, continuous	E2551	58731	no code
Nondependent opioid abuse, episodic	E2552	64382	no code
Nondependent opioid abuse NOS	E255z	69508	no code
[X]Mental and behavioural disorders due to use of opioids	Eu11.00	47335	no code
[X]Mental & behav dis due to use opioids: acute intoxication	Eu11000	42456	no code
X]Mental and behav dis due to use of opioids: harmful use	Eu11100	37568	no code
[X]Mental and behav dis due to use opioids: dependence syndrome	Eu11200	34249	no code
[X]Drug addiction - opioids	Eu11211	10538	no code
[X]Heroin addiction	Eu11212	4564	no code
[X]Mental and behav dis due to use opioids: withdrawal state	Eu11300	36241	no code
[X]Cold turkey, opiate withdrawal	Eu11311	25527	no code
[X]Men & behav dis due opioid: withdrawl state with delirium	Eu11400	97488	no code
[X]Mental & behav dis due to use opioids: psychotic disorder	Eu11500	50964	no code
[X]Mental and behav dis due to use opioids: amnesic syndrome	Eu11600	103991	no code
[X]Men & beh dis due opioids: resid & late-onset psychotic disease	Eu11700	29652	no code
[X]Men & behav dis due to use opioids: oth men & behav dis	Eu11y00	52739	no code
[X]Ment & behav dis due use opioids: unsp ment & behav dis	Eu11z00	91801	no code
Buprenorphine maintenance therapy	8B2M.00	47083	no code
Opioid agonist substitution therapy	8B2S.00	93980	no code
Opioid antagonist therapy	8B2T.00	93979	no code
Opioid drug dependence NOS	E240z	24441	no code

Appendix 7: Example STATA do files for CPRD cohort study

STATA Do Files

Demographics comparison

```
by case_status, sort: summarize yc_age, detail
ranksum yc_age, by (case_status)
tabulate ethnos_3cats case_status, chi2
tabulate yc_region case_status, chi2
tabulate yc_NSAIDs case_status, chi2
by case_status, sort: summarize yc_comorbidity_bnf, detail
ranksum yc_comorbidity_bnf, by (case_status)
proportion ethnos_3cats, over(case_status)
proportion yc_region_4cats , over(case_status)
proportion yc_NSAIDs , over(case_status)
proportion ever_smoking , over(case_status)
proportion ever_smoking
tabulate  ever_smoking case_status,  chi2
proportion ever_alcohol_use , over(case_status)
tabulate  ever_alcohol_use case_status, chi2
by case_status, sort : summarize BMIrecorded, detail
proportion bmi_cats
proportion bmi_overweight, over (case_status)
ranksum BMIrecorded, by (case_status)
```

Number of comorbid conditions and statistical comparison of groups

```
tabulate pre_menstruation
```

```
by case_status, sort: tabulate pre_menstruation
proportion pre_menstruation , over(case_status)
proportion pre_menstruation
by case_status, sort: tabulate thyroid
proportion thyroid , over(case_status)
tabulate thyroid case_status, cchi2 chi2
proportion thyroid
by case_status, sort: tabulate hypothyroid
proportion  hypothyroid  , over(case_status)
tabulate  hypothyroid  case_status, cchi2 chi2
proportion hypothyroid
by case_status, sort: tabulate hyperthyroid
proportion  hyperthyroid  , over(case_status)
tabulate  hyperthyroid  case_status, cchi2 chi2
proportion hyperthyroid
proportion  pituitary , over(case_status)
tabulate  pituitary case_status, cchi2 chi2
proportion  pituitary
proportion  adrenal , over(case_status)
tabulate  adrenal case_status, cchi2 chi2
proportion   adrenal
proportion  hypothalamic , over(case_status)
tabulate  hypothalamic case_status, cchi2 chi2
proportion   hypothalamic
proportion  obesity , over(case_status)
tabulate  obesity case_status, cchi2 chi2
```

```
proportion   obesity
proportion  lowBMI , over(case_status)
tabulate  lowBMI case_status, cchi2 chi2
proportion   lowBMI
proportion  structuralgynae , over(case_status)
tabulate  structuralgynae case_status, cchi2 chi2
proportion   structuralgynae
proportion  illegalopioid , over(case_status)
tabulate  illegalopioid case_status, cchi2 chi2
proportion   illegalopioid
```

Splitting BMI

```
egen bmi_overweight = cut (BMIrecorded), at (0,25,51)
recode bmi_overweight (0=0)
recode bmi_overweight (25=1)
recode bmi_overweight (.=2) [missing data]
proportion bmi_overweight , over(case_status)
tabulate  bmi_overweight case_status, cchi2 chi2
```

Creating Age groups

```
egen age_cats = cut (yc_age), at (18,26,36,46,56)
recode age_cats (18=1)
recode age_cats (26=2)
recode age_cats (36=3)
recode age_cats (46=4)
proportion  age_cats , over(case_status)
```

```
tabulate  age_cats case_status, cchi2 chi2
proportion  age_cats

Number of Practices included
sort pracid
gen long order=_n
by pracid (order), sort: gen y=_n==1
sort order
replace y=sum(y)
sum y

Proportion of outcomes five year follow up
generate outcome_5years=1 if post_menstruation==1 & time<=1825
recode outcome_5years (.=0)
tab outcome_5years
by case_status, sort: tabulate outcome_5years
proportion outcome_5years
proportion outcome_5years, over(case_status)
generate outcome_5years=1 if postlibido==1 & time<=1825
recode outcome_5years (.=0)
tab outcome_5years
by case_status, sort: tabulate outcome_5years
proportion outcome_5years
proportion outcome_5years, over(case_status)
generate outcome_5years=1 if postinfertility==1 & time<=1825
recode outcome_5years (.=0)
```

tab outcome_5years

by case_status, sort: tabulate outcome_5years

proportion outcome_5years

proportion outcome_5years, over(case_status)

generate outcome_5years=1 if postmenopause==1 & time<=1825

recode outcome_5years (.=0)

tab outcome_5years

by case_status, sort: tabulate outcome_5years

proportion outcome_5years

proportion outcome_5years, over(case_status)

Calculating rates/10000 person years (database time is in days)

stset time, id(patid) failure(post_menstruation ==1) exit(time 1825) scale(1)

by case_status, sort : stptime, by(age_cats) per (3650000)

stptime, by(age_cats) per (3650000)

Calculating number of people leaving cohort before 5 years for other reasons than outcomes

gen death_noevent = 1 if (deathstatus==1 & post_menstruation==0)

recode death_noevent (.=0)

tabulate death_noevent

gen leave_noevent = 1 if (post_menstruation==0 & fu_time <1825)

recode leave_noevent (.=0)

tabulate leave_noevent

gen leave_noevent = 1 if (post_menstruation==0 & fu_time <1825 & death_noevent==0)

Menstruation Cox Regression

```
stset time, id(patid) failure(post_menstruation==1) scale(1)

stsplit split, at (365,730,1835)

stcox case_status if split == 0 | split == 365 | split == 730

stcox case_status if split == 0

stcox case_status if split == 365

stcox case_status if split == 730

stcox case_status i.thyroid i.hypothyroid i.hyperthyroid i.ever_alcohol_use
i.ever_smoking i.bmi_overweight  i.lowBMI i.illegalopioid, tvc (c.yc_age
i.yc_NSAIDs_3cats i.structuralgynae i.pre_menstruation)

stcox case_status i.pre_menstruation i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0

stcox case_status i. pre_menstruation  i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 365

stcox case_status i.pre_menstruation  i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 730

stcox case_status i.pre_menstruation i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0 | split == 365 | split == 730

sort age_cats

by age_cats, sort : stcox case_status i.pre_menstruation i.thyroid i.hypothyroid
i.hyperthyroid i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI
i.structuralgynae i.illegalopioid c.yc_age i.ethnos_3cats if  split == 0 | split == 365 |
split == 730

by age_cats, sort : stcox case_status i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI  i.illegalopioid, tvc
(c.yc_age i.yc_NSAIDs_3cats i.pre_menstruation i.structuralgynae)

by age_cats, sort : stcox case_status if  split == 0 | split == 365 | split == 730
```

```
stcox case_status

estat phtest

stphplot, by(case_status)

sts graph, by(case_status)
```

Libido Cox Regression

```
stset time, id(patid) failure(postlibido==1) scale(1)

stsplit split, at (365,730,1835)

stcox case_status if split == 0 | split == 365 | split == 730

stcox case_status if split == 0

stcox case_status if split == 365

stcox case_status if split == 730

stcox case_status if split == 0 | split == 365 | split == 730, strata(obesity)

stcox case_status if split == 0, strata(obesity)

stcox case_status if split == 365, strata(obesity)

stcox case_status if split == 730, strata(obesity)

stcox case_status i.prelibido i.thyroid i.hypothyroid i.hyperthyroid i.ever_alcohol_use
i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae i.illegalopioid
i.yc_NSAIDs_3cats, tvc (c.yc_age)

stcox case_status i.prelibido i.thyroid i.hypothyroid i.hyperthyroid i.ever_alcohol_use
i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae i.illegalopioid
i.yc_NSAIDs_3cats c.yc_age if split ==0

stcox case_status i. prelibido  i.thyroid i.hypothyroid i.hyperthyroid i.ever_alcohol_use
i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae i.illegalopioid
i.yc_NSAIDs_3cats c.yc_age if split == 365

stcox case_status i.prelibido  i.thyroid i.hypothyroid i.hyperthyroid i.ever_alcohol_use
i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae i.illegalopioid
i.yc_NSAIDs_3cats c.yc_age if split == 730
```

```
stcox case_status i.prelibido i.thyroid i.hypothyroid i.hyperthyroid i.ever_alcohol_use
i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae i.illegalopioid
i.yc_NSAIDs_3cats c.yc_age if split == 0 | split == 365 | split == 730

sort age_cats

by age_cats : stcox case_status if split == 0 | split == 365 | split == 730

by age_cats : stcox case_status i.prelibido i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0 | split == 365 | split == 730

by age_cats : stcox case_status if split == 0

by age_cats : stcox case_status i.prelibido i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0

by age_cats : stcox case_status split == 365

by age_cats : stcox case_status i.prelibido i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 365

by age_cats : stcox case_status if split == 730

by age_cats : stcox case_status i.prelibido i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 730


stcox case_status

estat phtest

stphplot, by(case_status)

sts graph, by(case_status)


Cox Regression Infertility

stset time, id(patid) failure(postinfertility==1) scale(1)

stsplit split, at (365,730,1835)

stcox case_status if split == 0 | split == 365 | split == 730
```

```
stcox case_status if split == 0

stcox case_status if split == 365

stcox case_status if split == 730

stcox case_status if split == 0 | split == 365 | split == 730, strata(obesity)

stcox case_status if split == 0, strata(obesity)

stcox case_status if split == 365, strata(obesity)

stcox case_status if split == 730, strata(obesity)


stcox case_status i.preinfertility i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid c.yc_age, tvc (i.yc_NSAIDs_3cats)

stcox case_status i.preinfertility i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0

stcox case_status i. preinfertility  i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 365

stcox case_status i.preinfertility  i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 730

stcox case_status i.preinfertility i.ever_alcohol_use i.ever_smoking i.bmi_overweight
i.thyroid i.hypothyroid i.hyperthyroid i.lowBMI i.structuralgynae i.illegalopioid
i.yc_NSAIDs_3cats c.yc_age if split == 0 | split == 365 | split == 730

age_cats, sort

by age_cats : stcox case_status if split == 0 | split == 365 | split == 730

by age_cats : stcox case_status i.preinfertility  i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0 | split == 365 | split == 730

by age_cats : stcox case_status if split == 0

by age_cats : stcox case_status i.preinfertility i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0
```

```
by age_cats : stcox case_status if split == 365

by age_cats : stcox case_status i.preinfertility i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 365

by age_cats : stcox case_status if split == 730

by age_cats : stcox case_status i.preinfertility i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 730

stcox case_status  i.preinfertility i.thyroid i.hypothyroid i.hyperthyroid
i.bmi_overweight i.lowBMI i.ever_alcohol_use i.ever_smoking i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if age_cats==3 & split == 0


stcox case_status i.preinfertility i.thyroid i.hypothyroid i.hyperthyroid i.bmi_overweight
i.lowBMI i.ever_alcohol_use i.ever_smoking i.structuralgynae i.illegalopioid
i.yc_NSAIDs_3cats c.yc_age if age_cats==3 & split == 365

stcox case_status i.preinfertility i.thyroid i.hypothyroid i.hyperthyroid i.bmi_overweight
i.lowBMI i.ever_alcohol_use i.ever_smoking i.structuralgynae i.illegalopioid
i.yc_NSAIDs_3cats c.yc_age if age_cats==3 & split == 730

stcox case_status

estat phtest

stphplot, by(case_status)

sts graph, by(case_status)


Cox Regression Menopause

stset time, id(patid) failure(postmenopause==1) scale(1)

stsplit split, at (365,730,1835)

stcox case_status if split == 0

stcox case_status if split == 365

stcox case_status if split == 730

stcox case_status if split == 0 | split == 365 | split == 730
```

```
stcox case_status if end_date <= INDEXDATE + 1826, strata(obesity)

stcox case_status if split == 0, strata(obesity)

stcox case_status if split == 365, strata(obesity)

stcox case_status if split == 730, strata(obesity)

stcox case_status i.thyroid i.hypothyroid i.hyperthyroid i.ever_alcohol_use
i.ever_smoking i.bmi_overweight  i.lowBMI i.illegalopioid, tvc (i.yc_NSAIDs_3cats
i.premenopause c.yc_age i.structuralgynae)


stcox case_status i.premenopause i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0

stcox case_status i.premenopause i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 365

stcox case_status i.premenopause i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 730

stcox case_status i.premenopause i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0 | split == 365 | split ==730


sort age_cats

by age_cats : stcox case_status if split == 0 | split == 365 | split == 730

by age_cats : stcox case_status i.premenopause i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0 | split == 365 | split == 730

by age_cats : stcox case_status if split == 0

by age_cats : stcox case_status i.premenopause i.thyroid i.hypothyroid i.hyperthyroid
i.ever_alcohol_use i.ever_smoking i.bmi_overweight  i.lowBMI i.structuralgynae
i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 0

by age_cats : stcox case_status split == 365
```

by age_cats : stcox case_status i.premenopause i.thyroid i.hypothyroid i.hyperthyroid i.ever_alcohol_use i.ever_smoking i.bmi_overweight i.lowBMI i.structuralgynae i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 365

by age_cats : stcox case_status if split == 730

by age_cats : stcox case_status i.premenopause i.thyroid i.hypothyroid i.hyperthyroid i.ever_alcohol_use i.ever_smoking i.bmi_overweight i.lowBMI i.structuralgynae i.illegalopioid i.yc_NSAIDs_3cats c.yc_age if split == 730

estat phtest

stphplot, by(case_status)

sts graph, by(case_status)

proportion   postmenopause

proportion postmenopause, over(case_status)

SENSITIVITY ANALYSIS

FOR COMPLETE DATA ONLY

drop if ever_smoking==3

drop if ever_alcohol_use==3

drop if ethnos_3cats==3

drop if BMIaverage==.

drop if imd2010_5==.

duplicates tag match_pair , gen(tag)

drop if tag == 0

and repeat cox regression

FOR THOSE WITHOUT PRE_EXISTING CONDITIONS

Drop if prelibido==1

Drop if premenopause==1

Drop if premenstruation ==1

Drop if preinfertility==1

Duplicates tag match_pair, gen(tag)

Drop if tag == 0

Redo cox regression

FOR THOSE WITHOUT MENOPAUSE for SENSITIVITY ANALYSIS

drop if postmenopause == 1

drop if premenopause == 1

duplicates tag match_pair, gen(tag)

drop if tag == 0

Appendix 8: Screenshot of cohort study publication

EJP
European Journal of Pain

ORIGINAL ARTICLE

Increased risk of reproductive dysfunction in women prescribed long-term opioids for musculoskeletal pain: A matched cohort study in the Clinical Practice Research Datalink

E. Richardson, J. Bedson, Y. Chen, R. Lacey, K.M. Dunn

Research Institute for Primary Care & Health Sciences, Keele University, UK

Correspondence
Emily Richardson
E-mail: e.wersocki@keele.ac.uk

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Conflicts of interest
None declared.

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1 June 2018

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Abstract

Background: One-fifth of primary care attendees suffer chronic noncancer pain, with musculoskeletal conditions the leading cause. Twelve percent of patients with chronic noncancer pain are prescribed strong opioids. Evidence suggests long-term opioid use is related to hypogonadism in men, but the relationship in women is unclear. Our aim was to investigate reproductive dysfunction in women prescribed long-term opioids for musculoskeletal pain.

Methods: We undertook a matched (matched 1:1; for year of birth, year of start of follow-up and practice) cohort study of women aged 18–55 years old, with musculoskeletal pain and an opioid prescription in the Clinical Practice Research Datalink (a primary care database) between 2002 and 2013. Long-term opioid users (≥90 days) were compared with short-term opioid users (<90 days) for four reproductive conditions (abnormal menstruation, low libido, infertility and menopause) using Cox proportional hazards models.

Results: A total of 44,260 women were included; the median cohort age at baseline was 43 years (Interquartile Range 36–49). Long-term opioid use was associated with an increased risk of altered menstruation (hazard ratio 1.13 95% CI 1.05–1.21) and with an increased risk of menopause (hazard ratio 1.16 95% CI 1.10–1.23). No significant association was found for libido (hazard ratio 1.19 95% CI 0.96–1.48) or infertility (hazard ratio 0.82 95% CI 0.64–1.06).

Conclusions: The risk of menopause and abnormal menstruation was increased in long-term opioid users. This has implications for clinicians as reproductive dysfunction will need to be considered when prescribing long-term opioids to women with musculoskeletal conditions.

Significance: This is a large-scale cohort examining the relationship between long-term opioid use and reproductive dysfunction using a UK national primary care database. There is an increased risk of reproductive dysfunction associated with long-term opioid use.

1. Introduction

Chronic noncancer pain (CNCP) can be defined as any painful condition lasting for 3 months or more and not associated with neoplastic disease (cancer) (Chapman et al., 2010). Musculoskeletal (MSK) conditions are the leading cause of CNCP (Breivik et al., 2006). Over a fifth (22%) of patients attending primary care report CNCP, women are more commonly affected than men (Gureje et al., 1998).

Opioid prescribing has been increasing over the past 20 years and guidelines recommend their use as

Appendix 9 Cross-sectional study protocol

Opioids, Women and Libido

This protocol has regard for HRA guidance

Contents

Summary

Title: Sexual dysfunction in women receiving opioids for potentially painful musculoskeletal (MSK) conditions.
Short Title: Opioids, Women and Libido (OWL) Study
Protocol Version Number and Date: Protocol 1.0, 25/7/17
IRAS Project ID: 210681
Key Words: Opioids, Female Sexual Dysfunction, Libido, Adverse Events
Background: 22% of primary care attendees suffer chronic non-cancer pain (CNCP), 12-13% of these are prescribed opioids. Up to 20% of people consult with their GP each year with MSK conditions and opioids are often prescribed for the treatment of these conditions, in line with guidelines. Since the 1980s there has been a significant increase in opioid prescribing. Adverse effects are common in people taking opioids with up to 80% affected by at least one adverse effect. Long-term prescription opioid use in men and illegal opioid use in women can lead to reproductive and sexual problems (low libido, impotence), but there is a lack of evidence in women taking prescribed opioids. A comprehensive literature review found limited evidence of a potential relationship between opioids and reproductive and sexual dysfunction in women. A study in women using information from a primary care consultations database found an increased risk of menopausal symptoms and abnormal menstruation in long-term (>90 days) opioid users with potentially painful MSK conditions. However, there were low numbers of women within the cohort with a recorded diagnosis of infertility or low libido compared with what might be expected in the general population. This suggests a different approach is needed to investigate this area in future research.
Aim and objectives: The aim of this study is to investigate associations between opioid use and sexual dysfunction in women as characterised by low libido. Specific objectives are (1) to investigate the prevalence of low libido in women receiving opioids for MSK pain; (2) to compare the prevalence of low libido in women using long-term, and short-term opioids. Long-term opioid use is defined as 90 days of use if self-reported (or 3 prescriptions in 90 days identified from medical records) and short-term opioid use is anything less than this; (3) within women who are long-term opioid users, to compare the number with low libido according to the mode of opioid administration, either orally as a tablet or transdermal in the form of a patch; (4) within women who are long-term opioid users, to compare the number with low libido according to the total opioid dose each day using morphine equivalent dose (conversion of corresponding doses of different opioids to morphine doses using predefined conversion tables) with a doses of 20mg/day and higher representing the threshold between high and low dose opioids (defined based on previous epidemiological work of opioid adverse effects); and (5) to compare self-reported rates of low libido to those within the medical records.
Design: Cross-sectional postal survey

Study Population: Primary care consulters (women, aged 18-45 years old) presenting to General Practice with a Read Coded potentially painful MSK condition who are prescribed an opioid.
Sample Size: 316 responses required, 1000 participants will be contacted.
Data Collection: A single self-report postal questionnaire will be sent to eligible patients. Consent will be sought to access anonymised medical records for a full medication history, including all coded entries for low libido.
Outcome measures: Sexual dysfunction will be recorded using a previously validated measure STEFFI-5 (STEFFI is not an acronym but named after the common German girls name). The SF-12 will also be used to measure mental and physical health overall.
Analysis: Descriptive methods will be used to characterise the population and sub-groups of opioid users (short-term and long-term opioids). The characteristics will be compared using statistical tests (e.g. Chi-squared, Student's T test, Wilcoxon-Mann-Whitney). The prevalence of sexual dysfunction will be calculated. Comparison between different types of opioid users will be undertaken as logistic regression and produce odds ratios, this will be adjusted for confounding factors (e.g. age, depression status) and covariates (e.g. comorbidities, smoking and BMI). The comparison groups will be long-term vs short-term opioids, then within the long-term opioid user group if possible oral vs. transdermal and total morphine daily equivalent dose split at 20mg/day. P values of less than 0.05 will be taken as significant.

Background and Rationale

Background

Over 20% of primary care attendees report CNCP, with women affected more often than men (Gureje et al., 1998). 12% of all affected patients are prescribed opioids and women are more likely than men to start a new episode of opioid use (Bedson et al., 2016). One in five of the population attend primary care each year with a MSK condition and this accounts for one in seven primary care appointments (Jordan et al., 2006, 2010). Opioids are recommended in guidelines for use in MSK pain as part of a stepped approach to care (National Institute for Health and Care Excellence, 2014a, 2016). Since the late 1980s there has been a trend towards increased opioid prescribing (Caudill-Slosberg et al., 2004; Eriksen et al., 2006; Von Korff et al., 2008; Ruscitto et al., 2015; Sullivan et al., 2008; Zin et al., 2014). A recent UK observational database study showed a 38% increase in opioid prescribing from 2002 to 2009, with a prescribing rate of 31.2/10000 (95% CI 29.1-33.4) person years in women aged 18-44 years old; this increase is despite a Cochrane review showing only weak

evidence for their effectiveness (Bedson et al., 2016; Noble et al., 2010). Adverse effects are common among people taking opioids for the first time, with 80% of patients experiencing at least one, such as constipation, somnolence, nausea, vomiting, dizziness, itching, dependency, tolerance, addiction and opioid induced hyperalgesia (Baldini et al., 2012; Grady et al., 2002; Kalso et al., 2004; The British Pain Society, 2010).

Long-term prescription opioid use in men can cause decreased levels of sex hormones (in particular testosterone) leading to reproductive and sexual dysfunction; this is known as opioid induced androgen deficiency (OPIAD) (Abs et al., 2000; Aloisi et al., 2009; Benyamin et al., 2008; Daniell, 2002; Smith and Elliott, 2012). In women, it is recognised that illegal dependent opioid use (for instance heroin) can be associated with hypogonadism and reproductive and sexual dysfunction (low libido, sexual dysfunction, menopausal symptoms and absent or less frequent menstruation) (Brown and Zueldorff, 2007; Genazzani et al., 1993; Schmittner et al., 2005). The picture is less clear with respect to any association between prescription opioid use and reproductive/sexual dysfunction in women. Guidelines from the British Pain Society highlight possible reproductive and sexual adverse effects from using opioids in men and women as a concern but concluded that there was insufficient data to be able to quantify the risk associated with long-term opioids (The British Pain Society, 2010). A comprehensive systematic literature review undertaken of long-term opioid use in women with CNCP and reproductive and sexual dysfunction found 12 papers (small studies with 200 subjects in total). Although the evidence was of low quality and conflicting, the majority of studies found a link between opioid use (>30 days) and reproductive and sexual dysfunction (Wersocki et al., 2017).

A matched cohort study has been undertaken comparing women with potentially painful MSK conditions taking long-term (patients who receive three or more opioid prescriptions over 90 days or more) and short-term opioids (maximum of 2 opioid prescriptions in no more than 90 days) in a large electronic database containing information from GP practices, the Clinical Practice Research Datalink (CPRD) (Wersocki et al., 2016). The aim of the cohort study was to investigate the prevalence of reproductive and sexual dysfunction (altered menstruation, menopause, low libido and infertility) in women 18-55 years old taking long-term opioids for potentially painful MSK conditions. The cohort study also compared the risk of developing these conditions between long-term opioids users and short-term opioid users. The women all had a potentially painful MSK condition in order to make the cohort more homogenous and limit systematic differences between the two groups. This also addresses elements of indication bias as all the women were receiving the medication for the same indication however it does not address any potential differences in severity of disease. An increased risk of menopausal symptoms and altered menstruation (less frequent or absent menstruation) in women taking long-term opioids was found compared with women who had only received short-term opioids. One limitation of this database study was the small numbers of women reporting low libido and infertility, less than 1% of women had a coded diagnosis of low libido compared with population estimates of 20-40% (Dunn et al., 1998). Prevalence of infertility was 0.5% (0.5-0.6) with an expected prevalence in the general population of around 2%. However this is a global estimate and includes only women aged 20-44 years old who are exposed to the risk of pregnancy, so this may be in line with those estimates (Mascarenhas et al., 2012).

Rationale

The proposed cross-sectional study aims to investigate the relationship between opioid use and sexual dysfunction further. The study will focus on low libido in particular, as within the CPRD study prevalence of low libido was low when compared to population estimates, suggesting this methodological approach may not be most appropriate way to investigate this area. One of the possible reasons for this difference is that both women and clinicians find it difficult to discuss sexual health issues and as such they are often ignored (Montgomery, 2008). A cross-sectional study offers a straight forward approach for investigating low libido as it allows women to answer questions directly, however it will not be able to examine the issue of causality.

The cohort will include women aged 18-45 years old with a coded potentially painful MSK condition and a prescribed opioid in their electronic medical records. This upper age was selected to minimise the number of women in the perimenopause who were included in the study. Including women likely to be premenopausal was important as there is good evidence that libido decreases during the peri-menopausal period when compared to premenopausal women (Odds Ratio 2.6, 95% CI 0.6-10.8) and also decreases with increasing age (Hayes et al., 2008).The median age of the menopause in the UK is 52 years old (Hardy and Kuh, 2005). It is believed that hormonal changes characteristic of menopause start at around 45 years of age and symptoms of perimenopause start at a median age of 47.5 in white women in western countries (Gold, 2011). Potentially painful non-inflammatory MSK conditions were chosen to identify women as it is a common presenting complaint in primary care (1 in 7 consultations) and they represent a more homogenous group than women prescribed opioids for any indication (Jordan et al., 2010). This decreases systematic differences between different types of opioid use, and helps to limit confounding by indication.

This project will further investigate an area where there is a lack of evidence in the literature. There has been increasing opioid prescribing despite a lack of evidence for opioid effectiveness for CNCP and women are more likely than men to be prescribed opioids. This study will raise awareness within researchers and health professionals of the potential adverse effects of opioids.

Aims and Objectives

Aims

The primary aim of this study is to investigate associations between opioid use and sexual dysfunction in women with MSK conditions. Sexual dysfunction in this case will mean specifically low libido.

Objectives

5) To investigate the prevalence of low libido in women receiving opioids for MSK pain
6) To compare the prevalence of low libido in women using long-term, and short-term opioids. Long-term opioid use is defined as 90 days of use if self-reported (or 3 prescriptions in 90 days identified from medical records) and short-term opioid use is anything less than this.
7) Within women who are long-term opioid users, to compare the number with low libido according to the mode of opioid administration (tablets compared to patches)
8) Within women who are long-term opioid users, to compare the number with sexual dysfunction according to the total opioid dose each day will be compared, using total morphine equivalent dose and a cut-off point of ≥20mg/day between high and low dose opioids (Saunders et al., 2009).
9) To compare self-reported rates of low libido to those recorded within the medical records.

Study Methods

Design

The OWL study will be undertaken as a cross-sectional survey. Quantitative data will be collected using a single self-report postal questionnaire. Further information for comparison will be gained from medical records data linkage with patient consent. See Figure 1 for an illustration of recruitment and data collection procedures.

Study Population and Setting

Participants will be recruited from primary care. The participants will be identified from up to 20 UK primary care practices within the National Institute for Health Research Clinical Research Network (NIHR CRN) in the West Midlands. Women aged 18-45 years old who have a coded potentially painful MSK condition and have been prescribed an opioid within the last 6 months will be invited to participate.

Inclusion Criteria

- Women
- Aged 18-45 years old at the time of prescription
- Prescription of an opioid group 3 (e.g. codeine 15mg), group 4 (e.g. codeine 30mg) or group 5 (e,g oxycodone, morphine) which represents moderate to very strong opioids based on a previously developed consensus model of hierarchically arranged equipotent opioids (Bedson et al., 2010) within the 6 months prior to records search
- Painful MSK condition coded within the 6 months prior to records search

Exclusion Criteria

- Symptoms and signs indicating a serious pathology (cancer diagnosis) or red flag conditions requiring urgent medical attention (e.g. fractures, cauda equina)
- Inflammatory joint condition (e.g. rheumatoid arthritis or gout)
- Inability to read and speak English
- Vulnerable patients (assessed by GP), including patients on Quality and Outcomes Framework mental health or learning disabilities register.
- Pregnant
- Current HRT use
- Menopause

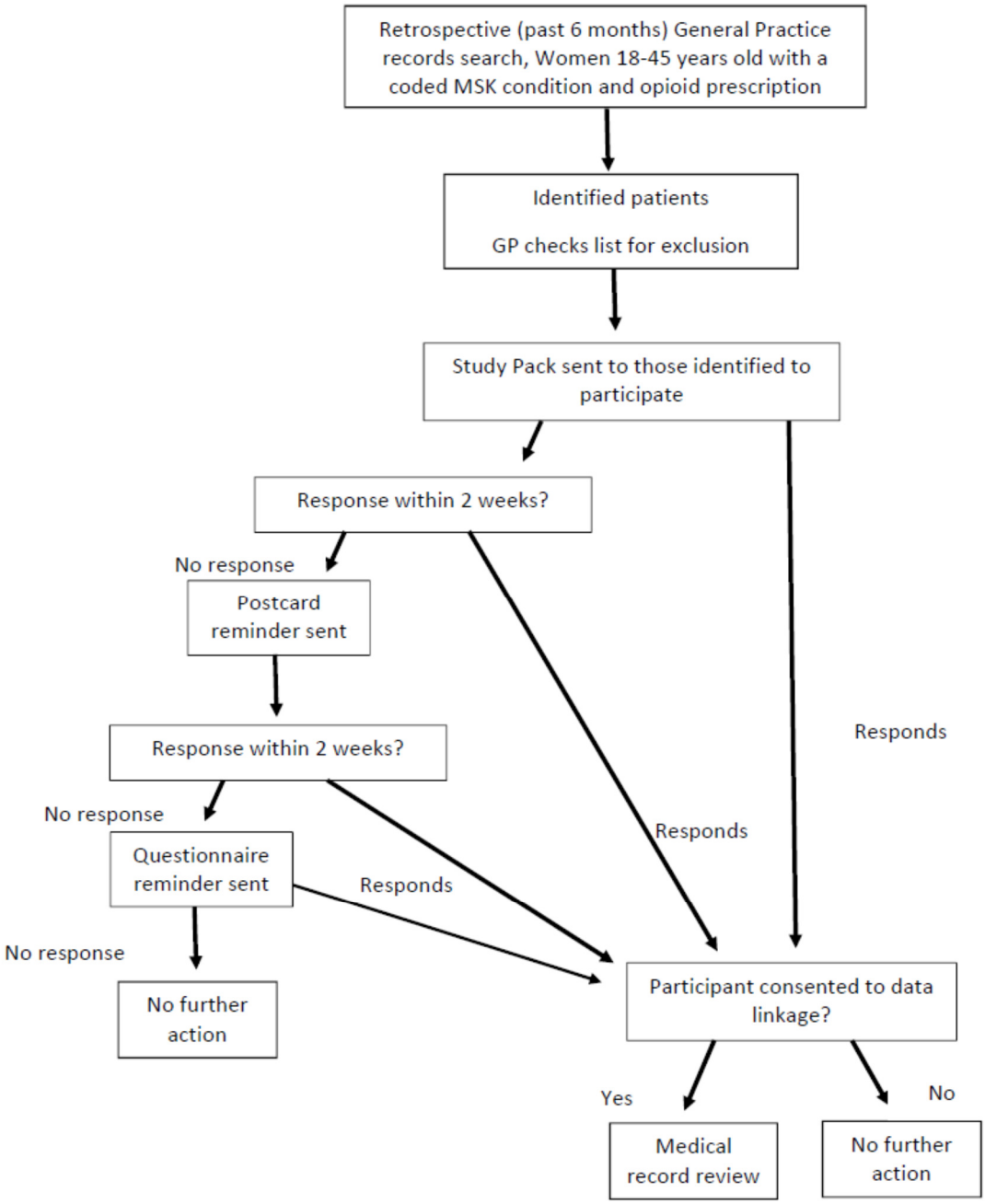
All patient facing material will be written in English (cover letters, questionnaires, reminders, and consent forms). It is therefore not possible to include any patients who cannot read or write English. All study documents will have contact details for the study coordinator if participants have any questions or difficulties completing the questionnaire or consent form.

Recruitment process

A retrospective notes search will be conducted on a single occasion in each practice looking at the previous 6 months to identify patients who are eligible for inclusion in the study. The search will identify women with an opioid prescription (group 3-5, moderate to very potent opioids as coded by Bedson et al. (Bedson et al., 2010)) and a coded painful MSK condition within the previous 6 months. GP Practice staff will identify potential participants and look at identifiable data. A database query will produce a list of names and addresses for each potentially eligible participant. This personal information will be used for mailing the study pack by the practice. GPs will be asked to screen the list of potential participants against study exclusion criteria and for suitability. Those women identified from the initial search and deemed to be appropriate by the GP will be mailed the study pack from the practice (the contact details will not leave the practice site, and will not be available to the study team). Each woman identified for participation in the study will be given a unique study identifier; this will be used to target reminders and for data linkage, these reminders will be sent from the general practice. The study pack will include a covering letter from the GP, a patient information leaflet, the questionnaire itself and a consent form for medical record review, the questionnaire and consent form will be marked with the participants unique study identifier. The patient information leaflet will contain all the relevant information required to allow the participant to give informed consent for review of their medical records. Following the study pack being mailed initially there will be a reminder system in place where a postcard reminder will be sent at 2 weeks if there is no response from the study participant, and a further questionnaire 2 weeks later as per research centre standards. This will be coordinated by the research team at Keele sending a list of unique study identifiers of those that have already replied with a completed questionnaire to the CRN and practice team, who will then send out reminders from the practice (Roberts et al., 1993). The reminders will be sent based on the basis of whether the participant has already responded and this will be based on the participant's unique study identifier which was

assigned during the identification stage. Consent for completion of the questionnaire will be assumed if a completed questionnaire is returned, however consent for medical records review and future contact will be through written consent.

Figure 1 Flow diagram of recruitment process and data collection



Baseline assessment

The participant will be mailed a questionnaire with the study pack, which will take approximately 20 minutes to complete. An overview of data collection is provided in Table 1. The questionnaire will include:

- Sociodemographic variables: age, work status, relationship status
- Lifestyle factors: alcohol, smoking, illegal drug use
- Height and weight (for BMI)
- Pain status (Chronic Pain Grade Questionnaire)
- Medication use (including current and recent opioid use, reasons for stopping medication and current contraception use)
- Sexual function assessed through the use of STEFFI-5 which is described below
- General mental and physical health assessed through the use of SF-12
- Past medical history including important conditions that are associated with low libido (anaemia, hypertension, depression, hysterectomy, diabetes, pelvic pain)

The primary study outcomes will be assessed via validated measures from previous studies. Sexual dysfunction will be assessed using STEFFI-5 which is a 5 question tool that screens for sexual dysfunction. STEFFI-5 was compared to the female sexual function index (FSFI) which is a widely used tool for those women already identified as having sexual dysfunction and had 83.1% sensitivity and 81.2% specificity for identifying women with sexual dysfunction (Kriston et al., 2010). The study will produce descriptive data on sexual dysfunction in this group and also undertake comparison between long-term and short-term opioid users. Comparison measures will also be undertaken within the long-term opioid user groups if possible, comparing transdermal and oral opioids and total daily morphine equivalent doses with ≥20mg/day as the cut off between high and low doses within the long-term opioids users. The study will provide the opportunity to compare self-reported problems to those within the medical records for those who consent to medical record review.

Pain will be assessed using the Chronic Pain Grade Questionnaire, a validated measure that assesses pain, currently and in the past 6 months (Von Korff et al., 1992). This has been validated for use in UK postal questionnaires through comparison with the SF-36 and had a Cronbach's alpha of >0.9 and item-total correlations of >0.68 for all items indicating good internal consistency and reliability (Smith et al., 1997).

STEFFI-5 and Chronic Pain Grade Questionnaire do not need a license for use as they are both freely available but do need to be cited. A license agreement (#CT184958 OP059432) has been agreed for use of the SF-12.

Medical Record review

For patients who have consented to medical record review, data will be extracted by practice staff regarding prescribed medication (including pain medication), recorded sexual dysfunction, age, height, weight, BMI, existing chronic diseases (for instance thyroid disease and pelvic pain) over the preceding 12 months. The medical records will be anonymised and assigned the unique study identifier by the practice staff that links with the corresponding questionnaire response. Each participant will be assigned a unique study identifier and this

will be used to link the questionnaire data to data from the medical record review. The study team will not have access to patient identifiable data from the medical records, the records will be anonymised prior to them being sent to the study team.

Table 23: Overview of Data Collection

	Questionnaire	Medical Record Review
Socio-demographic variables: age, work status, ethnicity	✓	✓
Lifestyle factors: smoking, alcohol, drug use, height, weight	✓	✓
Relationship status	✓	
Contraception	✓	✓
General Health (SF-12)	✓	
Opioid Use (including previous use and reasons for stopping)	✓	✓
Medication history	✓	✓
Sexual Health: 5 items (STEFFI-5)	✓	
Pain status (Chronic Pain Grade Questionnaire)	✓	
Current Medical Conditions	✓	✓

Data Management (entry, coding, cleaning, storage and confidentiality)

Questionnaire data will be entered into a specifically designed database, which will be tested *a priori* for reliability. The coding of questionnaire responses will be determined with input from the study statistician in accordance with the standard procedures within the Research Institute for Primary Care and Health Sciences, to facilitate data entry. The data will be entered from paper questionnaires and there will be cross checks (1 in 20) where a second member of the team will check the coding. Checks will also take place if there is any data outside the expected range. This will ensure reliability and quality assessment throughout the data input process.

Participant personal data (e.g. names and addresses) will be stored at the GP site and the study team will not access these, the study team will not have access to medical records unless the patient consents to medical records review and then will only receive anonymised records. Completed consent forms and questionnaires will be returned to the study team, the consent form will be separated from the questionnaire responses immediately on receipt by the study team. Consent forms with participant personal data will be stored separately to questionnaires. The questionnaire data will be stored in a password protected database accessible only to the study team. All paper documents (including consent forms and completed questionnaires) will be stored in locked cabinets within an alarmed building. Hard copies will be stored for a period of 5 years following completion of the study. All confidentiality arrangements adhere to the relevant regulations and guidelines (Data Protection Act 1998, Caldicott, GMC, MRC, Research Governance Framework) and Keele Clinical Trials Unit standard operating procedures (https://www.keele.ac.uk/kctu/services/). The Chief investigator has responsibility to ensure confidentiality procedures are followed and the integrity of the data.

Any future data sharing will follow the Institute's data sharing procedure (https://www.keele.ac.uk/kctu/datasharingresources/). All members of staff included in the study have explicit duties of confidentiality written into their employment contracts which are equivalent to those of NHS staff members.

Analysis

The data will entered into a database developed for the study and will be analysed using STATA (StataCorp, 2017). The postal survey will provide information on demographics, outcomes and confounding factors. The primary comparison will be between women receiving long-term opioids (>90 days opioid use) and women receiving short-term opioids to be in line with previous work. The demographics of the short-term and long-term opioid users will be described using means and standard deviations if normally distributed, and medians and interquartile ranges if non–parametric; where proportions are used, 95% Confidence Intervals (CI) will be presented. The demographics will be compared using basic statistical tests. Where two categorical variables are compared, a Chi-squared test will be used, and if the comparison is between a continuous variable, a student's t-test will be used if the data is parametric. Wilcoxon-Mann-Whitney test will be used for non-parametric data. The exposure (independent variable) of interest is opioid use. The outcome (dependent variable) will be sexual dysfunction in this case low libido. The prevalence of women reporting low libido will be calculated using proportions with 95% CIs. Comparison of the proportions of women reporting low libido between long-term and short-term opioids users (strength and mode of administration (oral or transdermal) will also be used for comparisons) will be done with chi-squared statistics. The association between the dependent variable (low libido) and the independent variable (opioid use long-term vs. short-term) will be expressed as odds ratios with 95% CIs. As this is a cross-sectional study we will not be able to estimate cause and effect but will describe any associations. Adjustment for potential confounders will be done through use of logistic regression which will provide adjusted odds ratios. Including age in the logistic regression is particularly important as there is evidence that libido decreases with age (Hayes et al., 2008). P values of

less than 0.05 (two sided tests) will be taken as significant. If there are sufficient numbers the above will be repeated comparing transdermal and oral opioids and also total morphine daily equivalent dose divided at a dose of ≥20mg/day for high and low doses (Saunders et al., 2009). Morphine daily equivalent doses will be calculated based on the patients reported usage and then converted into morphine equivalents (the corresponding dose of different opioids to morphine) using predefined conversion tables developed by von Korff et al. for the CONSORT study (Von Korff et al., 2008).

Sample size

A sample size of 1,000 participants has been calculated. The sample size calculation was based on unpublished data from a postal questionnaire by Dunn et al (1998) which found an odds ratio of sexual dysfunction in those taking opioids compared to those without opioids of 2.2 (based on 31% of opioid users an 17% of non-opioid users being affected by sexual dysfunction). This is a best estimate based on the available evidence using a two sided 95% significance level, a power of 80% and a ratio of 1:1 for comparison groups with primary comparison between long-term and short-term opioid users; the calculation estimated a sample size of 316 women. The same study asking about sexual problems in the general population in 1998 had a response rate of 49% in women of all ages but the response rate in those less than 57 years of age was 43% (Dunn et al., 1998). Sensitive topics are widely believed to cause a lower response rate; a Cochrane review found an odds ratio of 0.94 (95% CI 0.88-1.0) when sensitive questions were included (Edwards et al., 2009). Based purely on the sample size calculation of 316 and an expected response rate of 43% a total sample size of 735 women would be employed. It is likely that the response rate will be lower in this age range of participants. The national census which has excellent response rates had a response rate of 10% less in women aged 20-24 years old compared with 98% in women aged 60-64 years old; if this 10% decrease in response rate is taken into account the study would require a sample size of 957, which we adjusted to 1000 to help to ensure adequate response rate (Office for National Statistics, 2015).

User Involvement

The Research Institute for Primary Care and Health Sciences has an active Research User Group (RUG) which advises and provides feedback on research projects. The RUG unfortunately does not have any female members between 18 and 45 years old so novel methods will need to be used to engage this group of women. Steps have been taken to engage women in the appropriate age group through posting on UK pain support websites (painsupport.co.uk and painconcern.org.uk). Those women that responded were included and helped to support the study via either email, or an online forum (closed Facebook group), and if needed by face to face contact via skype. The women provided feedback on the study pack including the covering letter and questionnaire. The women reviewed the final version of the questionnaire for face validity prior to sending out. Results will be

reported to those who have contributed and they will be included in plans for dissemination of results if they wish to be.

Ethical Considerations

The main ethical consideration is the questionnaire itself as it will contain potentially sensitive questions regarding relationships and sexual health. To minimise any potential distress, the number of questions will be minimised and they will be introduced in a sensitive manner. All study documents will have contact details for the study coordinator if participants have any questions regarding the study. Contact details will also be provided in the event the questionnaire causes any distress, both MIND's contact number and advice on contacting their own GP. The questionnaire will be confidential and questionnaires will be anonymised. The participants will be identified with a unique study identifier in order to facilitate data linkage to medical records if participants consent. The study team will not have access to patient identifiable data at the identification and mailing stage as this will be held at the practice site. The study team will only hold patient identifiable data in the form of consent forms, these will be stored in a locked cabinet separately to the questionnaire responses.

Study team and organisation

Study Team

Table 2: Study Team

Role	Name
Lead Supervisor and Data Custodian	John Bedson
Chief Investigator, Keele University	Emily Wersocki
Study Coordinator, Keele University	Emily Wersocki
Statistical Support	Ying Chen
Co-Applicant	Rosie Lacey

Study Sponsor

Sponsor Organisation: Keele University

Contact on behalf of the sponsor:

Dr Clark Crawford, Head of Research Integrity, Directorate of Engagement and Partnerships, IC2 Building, Keele University, Staffs, ST5 5NH

Dissemination

This study represents an opportunity to provide new evidence regarding possible sexual adverse effects of opioids. Previous papers by the study team looking at the area of adverse effects of opioids have been published in international journals. This area of research is topical and is likely to generate interest. The findings of the study will be presented at a national conference and published within a peer reviewed academic journal. The dissemination will be discussed with the Patient Public Involvement and Engagement group (PPIE) established for this project via online contact (either Skype, email or Facebook) to see if they have any other important ideas. The results will also support a project being undertaken by the evidence based medicine group at Keele to provide a decision making aid for opioid prescribing to be used by clinicians and patients.

Funding Source

The study is funded by Professor Christian Mallen's NIHR Professorship.

References

Appendix 10: PPIE recruitment leaflet

For more information please contact:

Adele Higginbottom (Patient and Public Involvement Project Coordinator)
a.higginbottom@keele.ac.uk
01782 734844

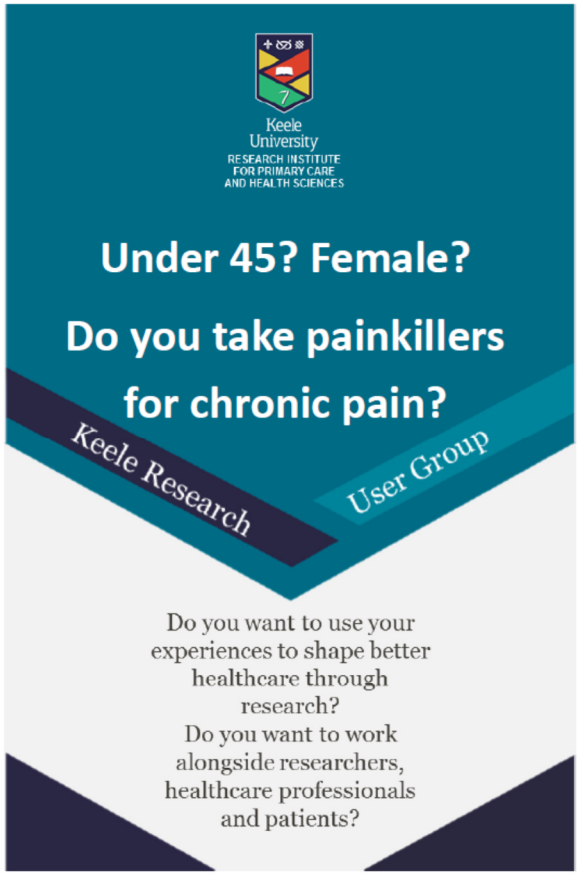
Or

Laura Campbell (User Support Worker in Research and Implementation and PPIE Knowledge Broker)
l.campbell@keele.ac.uk
01782 734727

Arthritis Research UK Primary Care Centre,
Research Institute for Primary Care & Health Sciences,
Keele University,
Staffordshire, ST5 5BG

Arthritis Research UK | primary care centre

PRIMARY CARE RESEARCH CONSORTIUM



Keele University Patient and Public Involvement and Engagement

Chronic Pain Research at Keele University

What is the Research User Group?

Patient and Public Involvement and Engagement is a key component of the work carried out at the Research Institute for Primary Care and Health Sciences at Keele University.
Members of the public, patients and carers are invited to discuss and have input on research studies at various points, from the initial development of an idea for research, right through to the dissemination of findings.
At Keele our research covers a broad range of musculoskeletal, chronic pain and mental health conditions and we aim to gather evidence so that future treatments are most likely to be of benefit.

Our research is most likely to be effective, appropriate and relevant if the public are actively working alongside researchers—*and that's where you come in.*

How can I help?

If you are a woman aged 45 or less we would like to hear from you. We would like to invite you to help us with a project we are designing to look at the possible side effects of painkillers in women of child bearing age.

What does it involve?

You will be asked to attend a meeting with other women with pain receiving prescription painkillers. During the meeting there will be refreshments and a break. We hope to have 6-10 women with chronic pain who are using or have used opioid painkillers. We will discuss our research ideas with you and ask for input into the survey design. It is likely there will be a further meetings to discuss the final survey, the results and ideas to spread these results .

What is the project?

This project aims to look at the possible side effects of strong painkillers called opioids. We are particularly interested in whether these types of medications can affect women's sexual and reproductive health. Opioids are morphine-like painkillers e.g. Codeine, Co-codamol, Dihydrocodeine, Co-dydramol, Tramadol, Fentanyl and Buprenorphine (BuTrans) patches, Morphine and Oxycodone (Oxycontin). We plan to send a survey to women receiving these types of medication and want your help with the questions we ask.

You will help our research to: Be understandable and relevant to people. Stay on track We will help, guide and support you as needed. The RUG group is not about being involved as a participant in a study, it is about being a lay advisor to researchers

Appendix 11: Ethical approval for cross-sectional study

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

Dr Emily Wersocki
NIHR In Practice Fellow
Keele University
Research Institute for Primary Care and Health Sciences
Keele University
Staffordshire
ST5 5BG

West of Scotland REC 5
West of Scotland Research Ethics Service
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SJ

Date 01 September 2017

Direct line 0141 232 1809
E-mail WoSREC5@ggc.scot.nhs.uk

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

Dear Dr Wersocki

Study title: **Long-term opioids in women with musculoskeletal pain in primary care and associated sexual dysfunction: A cross-sectional survey.**
REC reference: **17/WS/0182**
Protocol number: **RG-0161-17**
IRAS project ID: **210681**

Thank you for your letter of 29 August 2017, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]		28 June 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Keele University Insurance/Indemnity Policy]	1.1	31 July 2017
IRAS Application Form [IRAS_Form_02082017]		02 August 2017
Letter from funder [Confirmation of NIHR Funding]		
Letter from sponsor [Sponsorship Confirmation letter]		27 July 2017
Letters of invitation to participant [Invitation letter]	1.0	15 June 2017
Non-validated questionnaire [OWL questionnaire]	1.1	23 August 2017
Other [Postcard reminder]	1.0	26 July 2017
Other [Delegation of Sponsorship functions]	1.0	27 July 2017
Other [Response Letter to REC]		29 August 2017
Participant consent form [OWL consent form]	1.1	29 August 2017
Participant information sheet (PIS) [OWL Patient Information sheet]	1.1	29 August 2017
Referee's report or other scientific critique report [Outcome of Independent Peer Review]	1.0	16 June 2017
Research protocol or project proposal [OWL protocol]	1.1	23 August 2017
Summary CV for Chief Investigator (CI) [EW 2 page CV]		26 July 2017
Summary CV for supervisor (student research) [Summary CV RL]		
Summary CV for supervisor (student research) [CV YC]		
Summary CV for supervisor (student research) [CV JB]		26 June 2017
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Study flow chart]	1.0	19 April 2017

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and

the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/WS/0182	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

SMacgregor

for
Canon Matt McManus
Vice-Chair

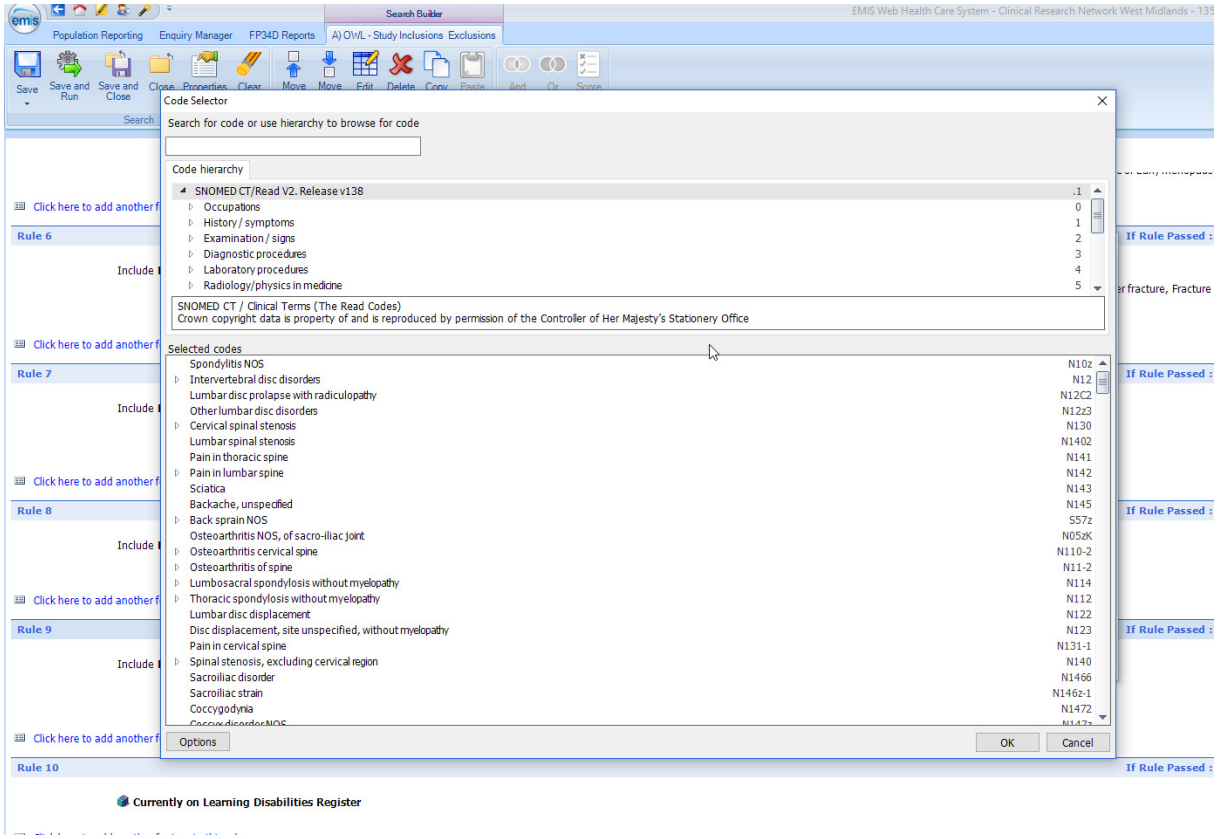
Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

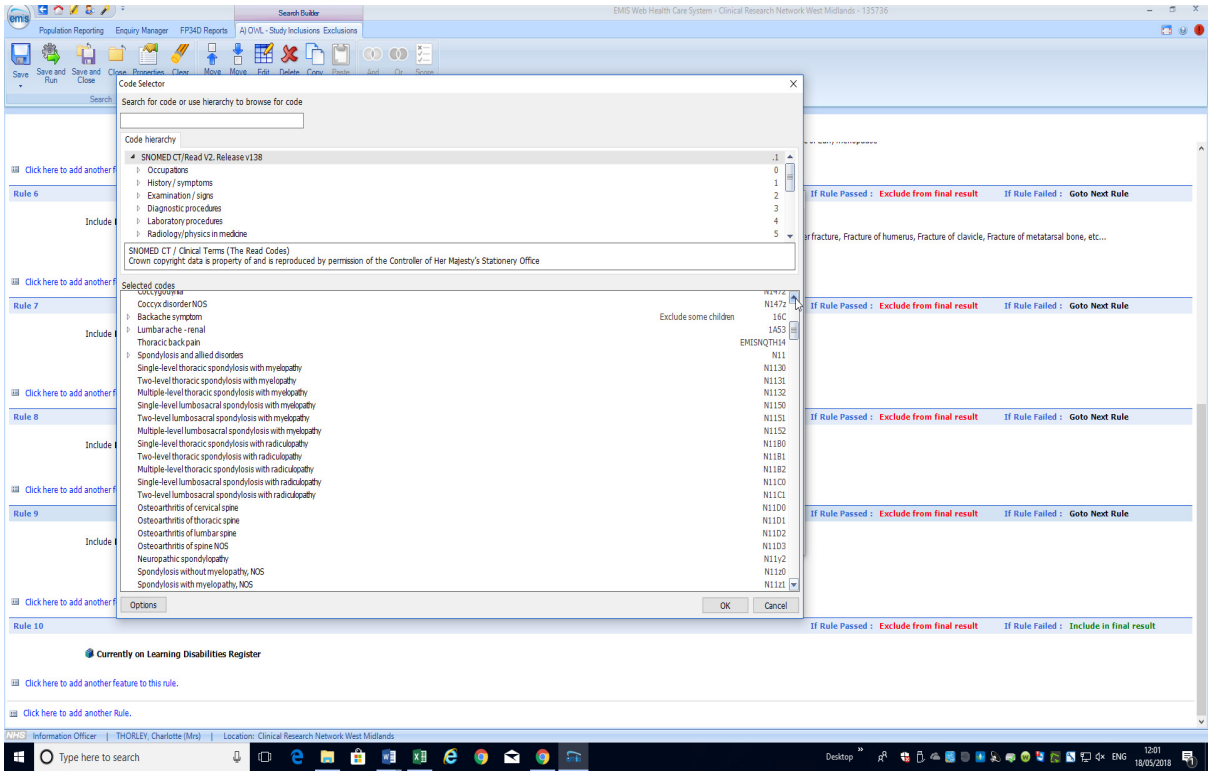
"After ethical review – guidance for researchers"

Copy to: Dr Clark Crawford, Keele University
Christine Woolven, CRN West Midlands

Appendix 12: Example codes used by CRN:WM for identification of participants for cross-sectional study

Inclusion Criteria

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Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2. Release v138
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
Crown copyright data is property of and is reproduced by permission of the Controller of Her Majesty's Stationery Office
Selected codes
Coccyx disorder NOS N147z
Backache symptom Exclude some children 16C
Lumbar ache - renal 1A53
Thoracic back pain EMISNQTH14
Spondylosis and allied disorders N11
Single-level thoracic spondylosis with myelopathy N1130
Two-level thoracic spondylosis with myelopathy N1131
Multiple-level thoracic spondylosis with myelopathy N1132
Single-level lumbosacral spondylosis with myelopathy N1150
Two-level lumbosacral spondylosis with myelopathy N1151
Multiple-level lumbosacral spondylosis with myelopathy N1152
Single-level thoracic spondylosis with radiculopathy N11B0
Two-level thoracic spondylosis with radiculopathy N11B1
Multiple-level thoracic spondylosis with radiculopathy N11B2
Single-level lumbosacral spondylosis with radiculopathy N11C0
Two-level lumbosacral spondylosis with radiculopathy N11C1
Osteoarthritis of cervical spine N11D0
Osteoarthritis of thoracic spine N11D1
Osteoarthritis of lumbar spine N11D2
Osteoarthritis of spine NOS N11D3
Neuropathic spondylopathy N11y2
Spondylosis without myelopathy, NOS N11z0
Spondylosis with myelopathy, NOS N11z1
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
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If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
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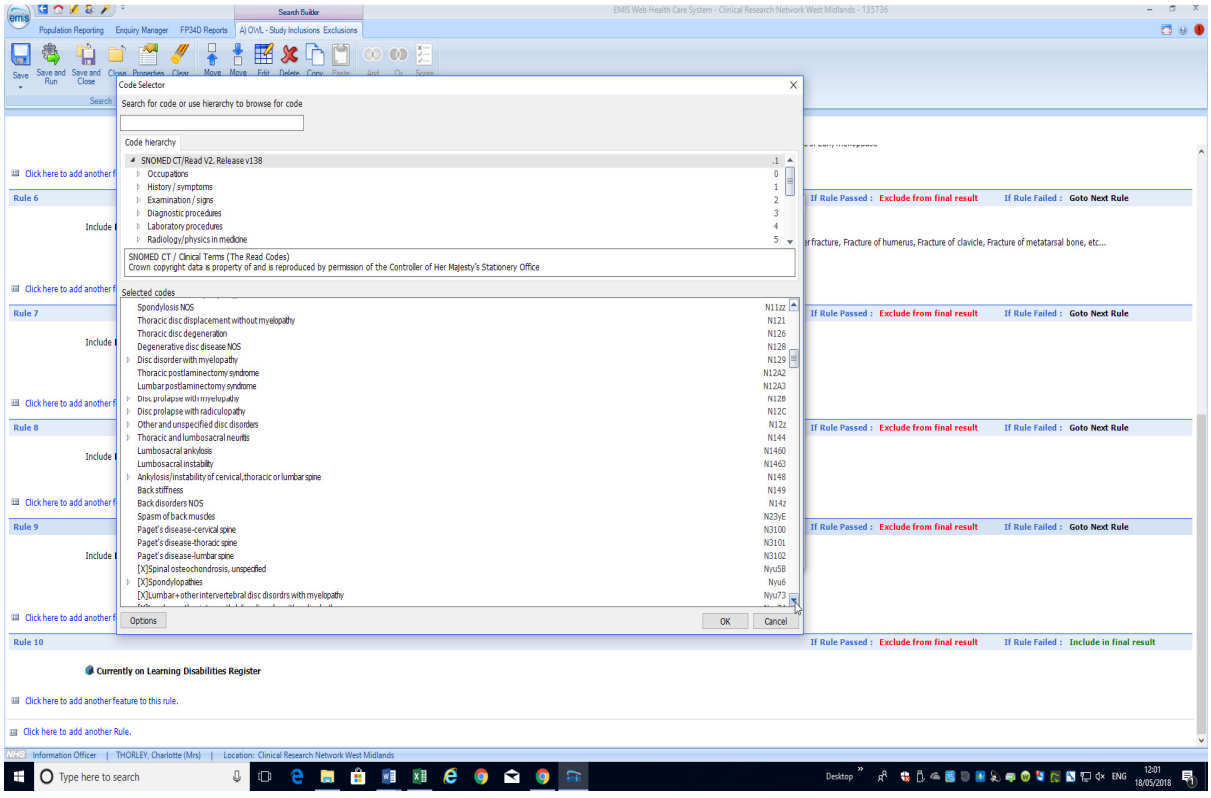
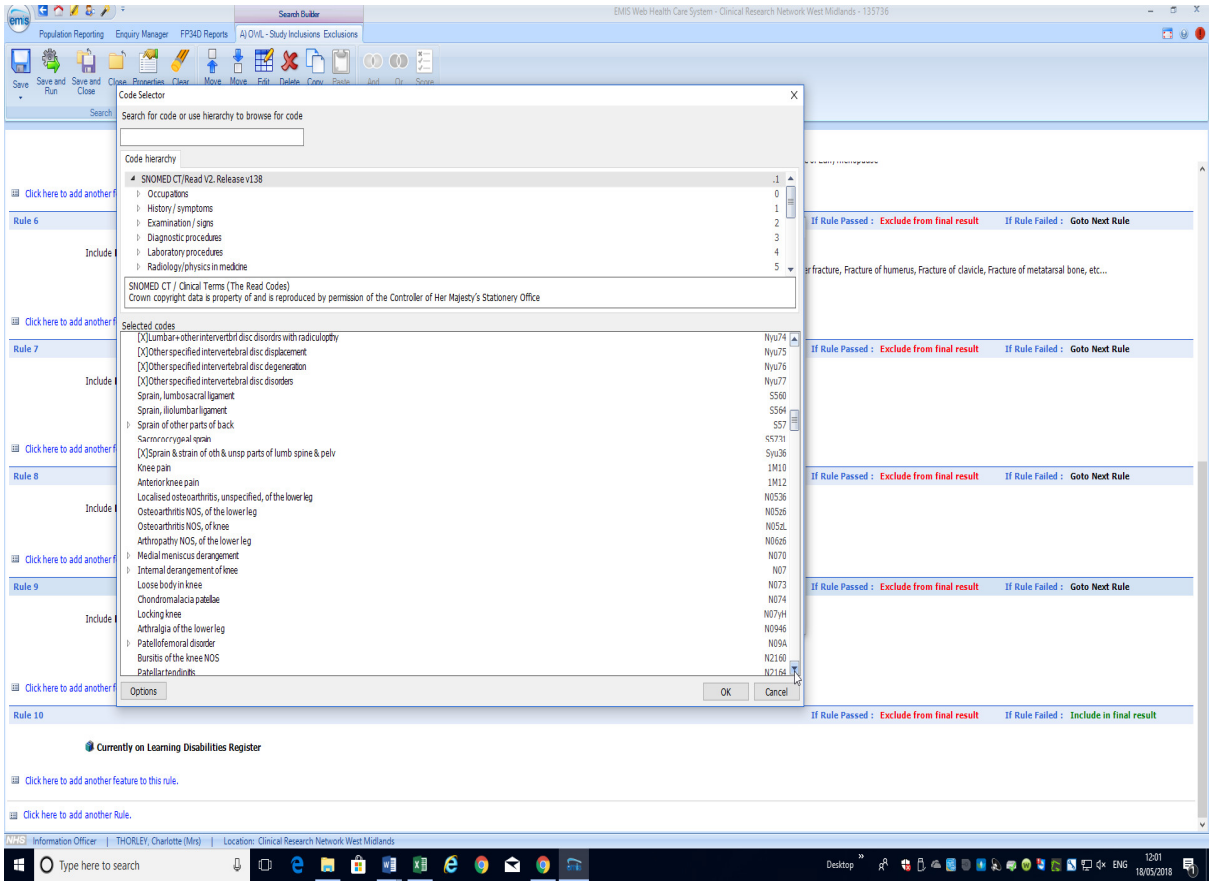
Click here to add another Rule.


Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2. Release v138
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
Crown copyright data is property of and is reproduced by permission of the Controller of Her Majesty's Stationery Office
Selected codes
Spondylosis NOS N11zz
Thoracic disc displacement without myelopathy N121
Thoracic disc degeneration N126
Degenerative disc disease NOS N128
Disc disorder with myelopathy N129
Thoracic postlaminectomy syndrome N12A2
Lumbar postlaminectomy syndrome N12A3
Disc prolapse with myelopathy N12B
Disc prolapse with radiculopathy N12C
Other and unspecified disc disorders N12z
Thoracic and lumbosacral neuritis N144
Lumbosacral ankylosis N1460
Lumbosacral instability N1463
Ankylosis/instability of cervical, thoracic or lumbar spine N148
Back stiffness N149
Back disorders NOS N14z
Spasm of back muscles N23yE
Paget's disease-cervical spine N3100
Paget's disease-thoracic spine N3101
Paget's disease-lumbar spine N3102
[X]Spinal osteochondrosis, unspecified Nyu5B
[X]Spondylopathies Nyu6
[X]Lumbar+other intervertebral disc disorders with myelopathy Nyu73
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.


Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2. Release v1.38
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
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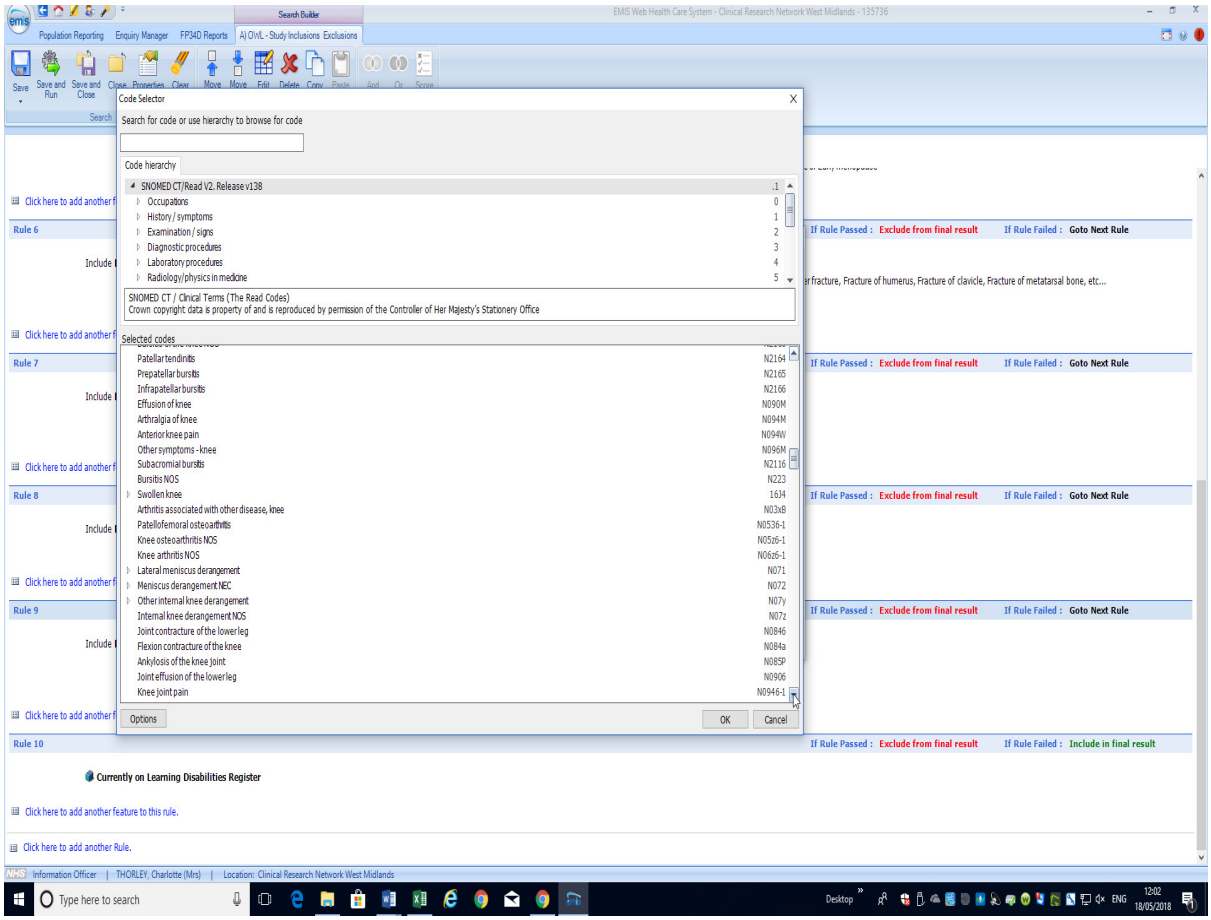
Selected codes
[X]Lumbar+other intervertbrl disc disordrs with radiculopthy
[X]Other specified intervertebral disc displacement
[X]Other specified intervertebral disc degeneration
[X]Other specified intervertebral disc disorders
Sprain, lumbosacral ligament
Sprain, iliolumbar ligament
Sprain of other parts of back
[X]Sprain & strain of oth & unsp parts of lumb spine & pelv
Knee pain
Anterior knee pain
Localised osteoarthritis, unspecified, of the lower leg
Osteoarthritis NOS, of the lower leg
Osteoarthritis NOS, of knee
Arthropathy NOS, of the lower leg
Medial meniscus derangement
Internal derangement of knee
Loose body in knee
Chondromalacia patellae
Locking knee
Arthralgia of the lower leg
Patellofemoral disorder
Bursitis of the knee NOS
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.


Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2, Release v138
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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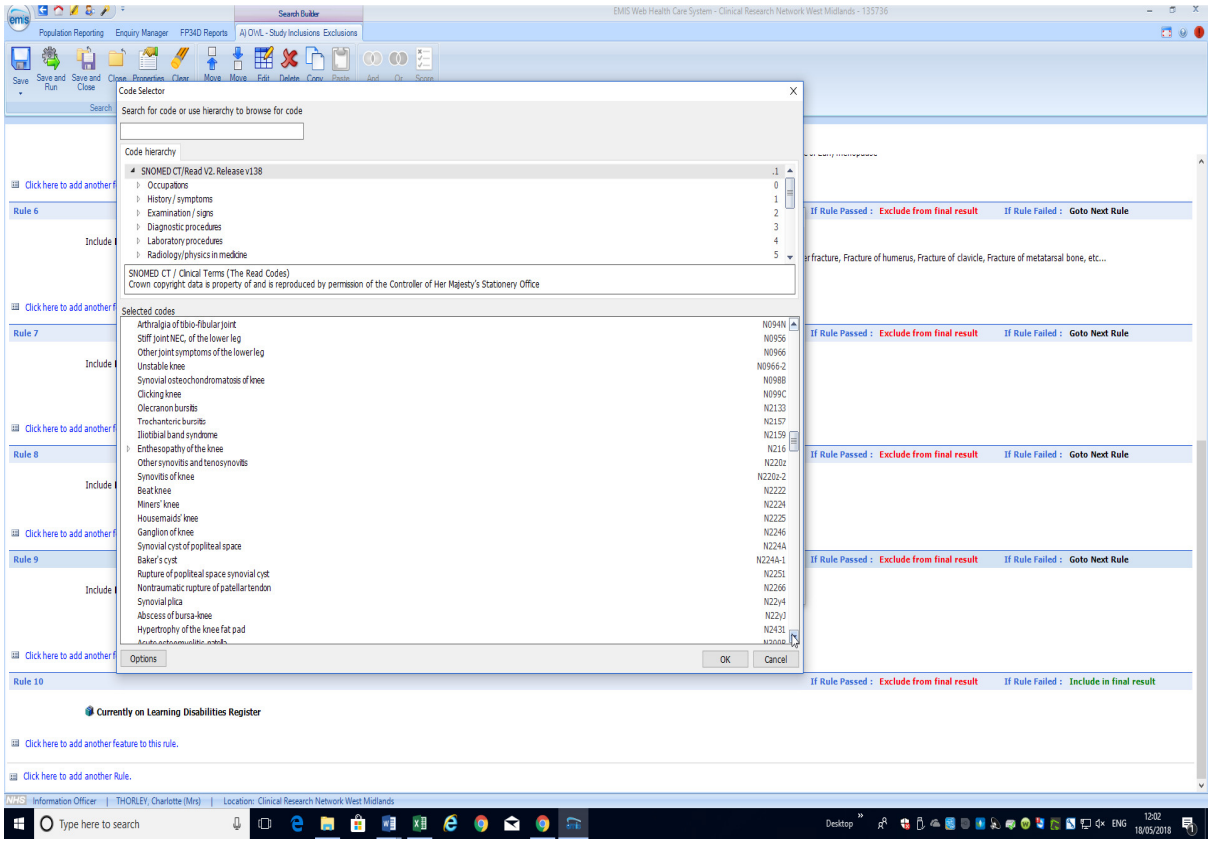
Selected codes
Patellar tendinitis
Prepatellar bursitis
Infrapatellar bursitis
Effusion of knee
Arthralgia of knee
Anterior knee pain
Other symptoms - knee
Subacromial bursitis
Bursitis NOS
Swollen knee
Arthritis associated with other disease, knee
Patellofemoral osteoarthritis
Knee osteoarthritis NOS
Knee arthritis NOS
Lateral meniscus derangement
Meniscus derangement NEC
Other internal knee derangement
Internal knee derangement NOS
Joint contracture of the lower leg
Flexion contracture of the knee
Ankylosis of the knee joint
Joint effusion of the lower leg
Knee joint pain
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.


Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2, Release v138
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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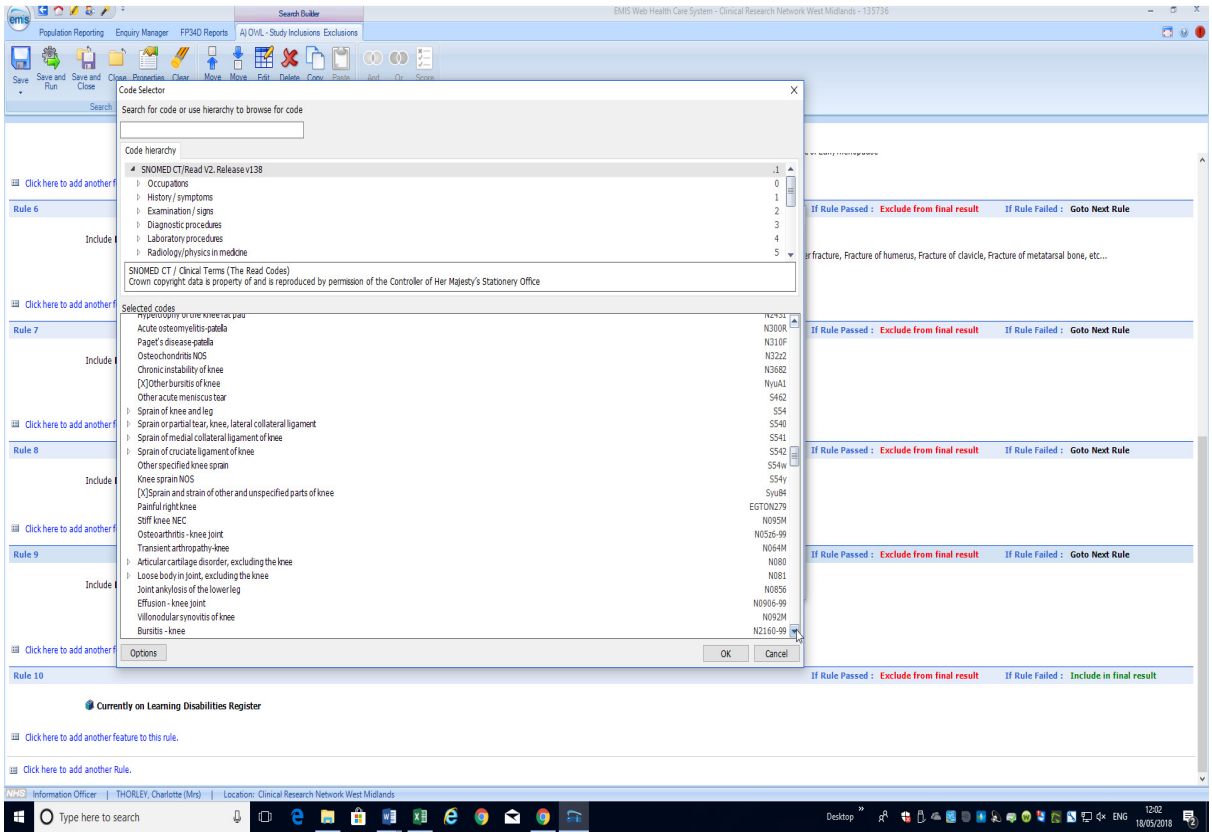
Selected codes
Arthralgia of tibio-fibular joint
Stiff joint NEC, of the lower leg
Other joint symptoms of the lower leg
Unstable knee
Synovial osteochondromatosis of knee
Clicking knee
Olecranon bursitis
Trochanteric bursitis
Iliotibial band syndrome
Enthesopathy of the knee
Other synovitis and tenosynovitis
Synovitis of knee
Beat knee
Miners' knee
Housemaids' knee
Ganglion of knee
Synovial cyst of popliteal space
Baker's cyst
Rupture of popliteal space synovial cyst
Nontraumatic rupture of patellar tendon
Synovial plica
Abscess of bursa-knee
Hypertrophy of the knee fat pad
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.


Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2, Release v1.38
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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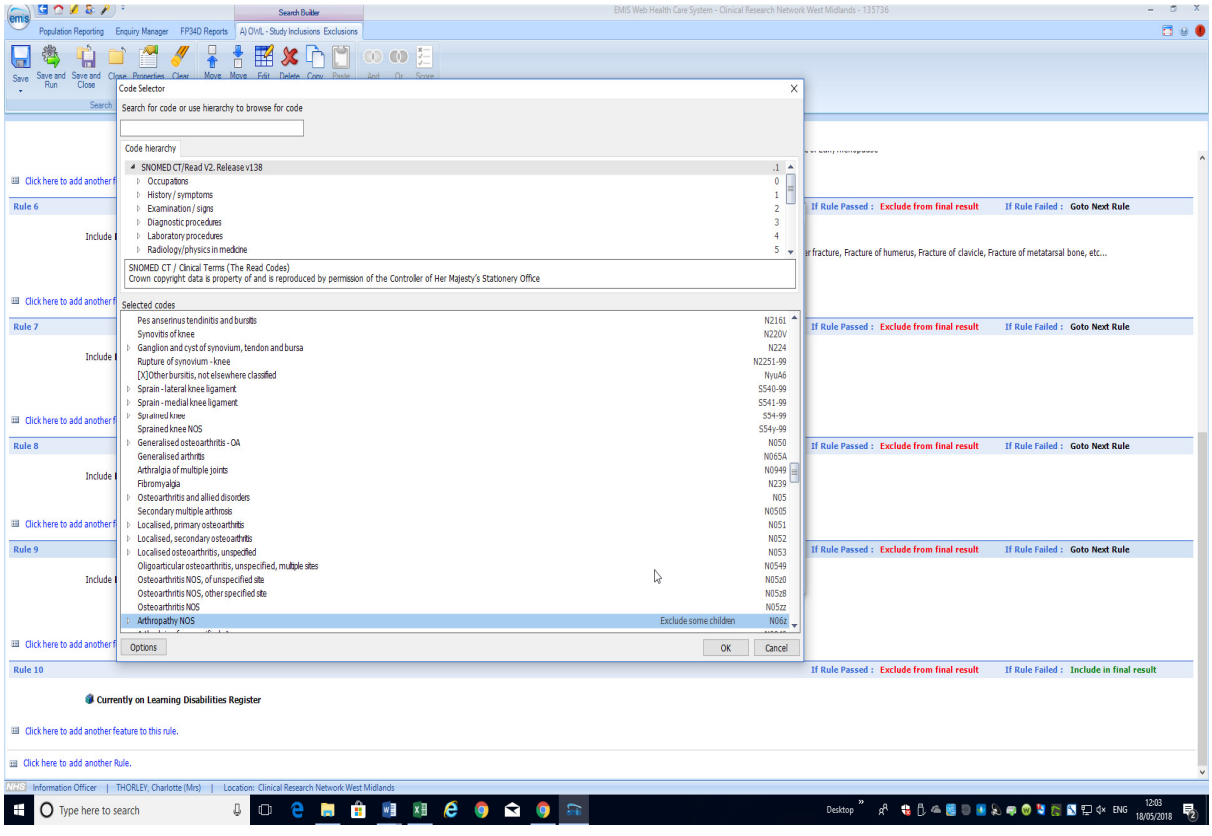
Selected codes
Acute osteomyelitis-patella
Paget's disease-patella
Osteochondritis NOS
Chronic instability of knee
[X]Other bursitis of knee
Other acute meniscus tear
Sprain of knee and leg
Sprain or partial tear, knee, lateral collateral ligament
Sprain of medial collateral ligament of knee
Sprain of cruciate ligament of knee
Other specified knee sprain
Knee sprain NOS
[X]Sprain and strain of other and unspecified parts of knee
Painful right knee
Stiff knee NEC
Osteoarthritis - knee joint
Transient arthropathy-knee
Articular cartilage disorder, excluding the knee
Loose body in joint, excluding the knee
Joint ankylosis of the lower leg
Effusion - knee joint
Villonodular synovitis of knee
Bursitis - knee
Options
OK
Cancel
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.


Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2, Release v1.38
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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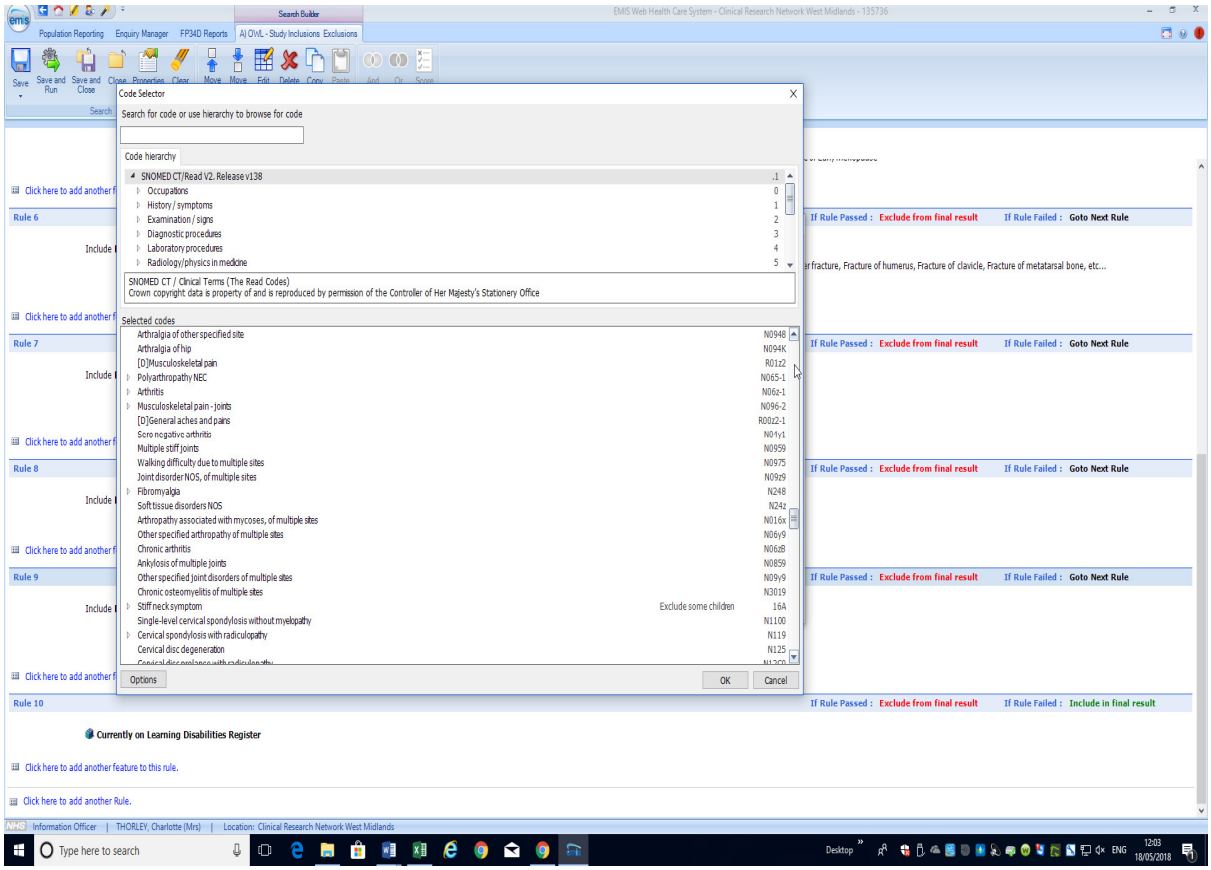
Selected codes
Pes anserinus tendinitis and bursitis
Synovitis of knee
Ganglion and cyst of synovium, tendon and bursa
Rupture of synovium - knee
[X]Other bursitis, not elsewhere classified
Sprain - lateral knee ligament
Sprain - medial knee ligament
Sprained knee NOS
Generalised osteoarthritis - OA
Generalised arthritis
Arthralgia of multiple joints
Fibromyalgia
Osteoarthritis and allied disorders
Secondary multiple arthrosis
Localised, primary osteoarthritis
Localised, secondary osteoarthritis
Localised osteoarthritis, unspecified
Oligoarticular osteoarthritis, unspecified, multiple sites
Osteoarthritis NOS, of unspecified site
Osteoarthritis NOS, other specified site
Osteoarthritis NOS
Arthropathy NOS
Exclude some children
Options
OK
Cancel
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.


Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2. Release v138
Occupations
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Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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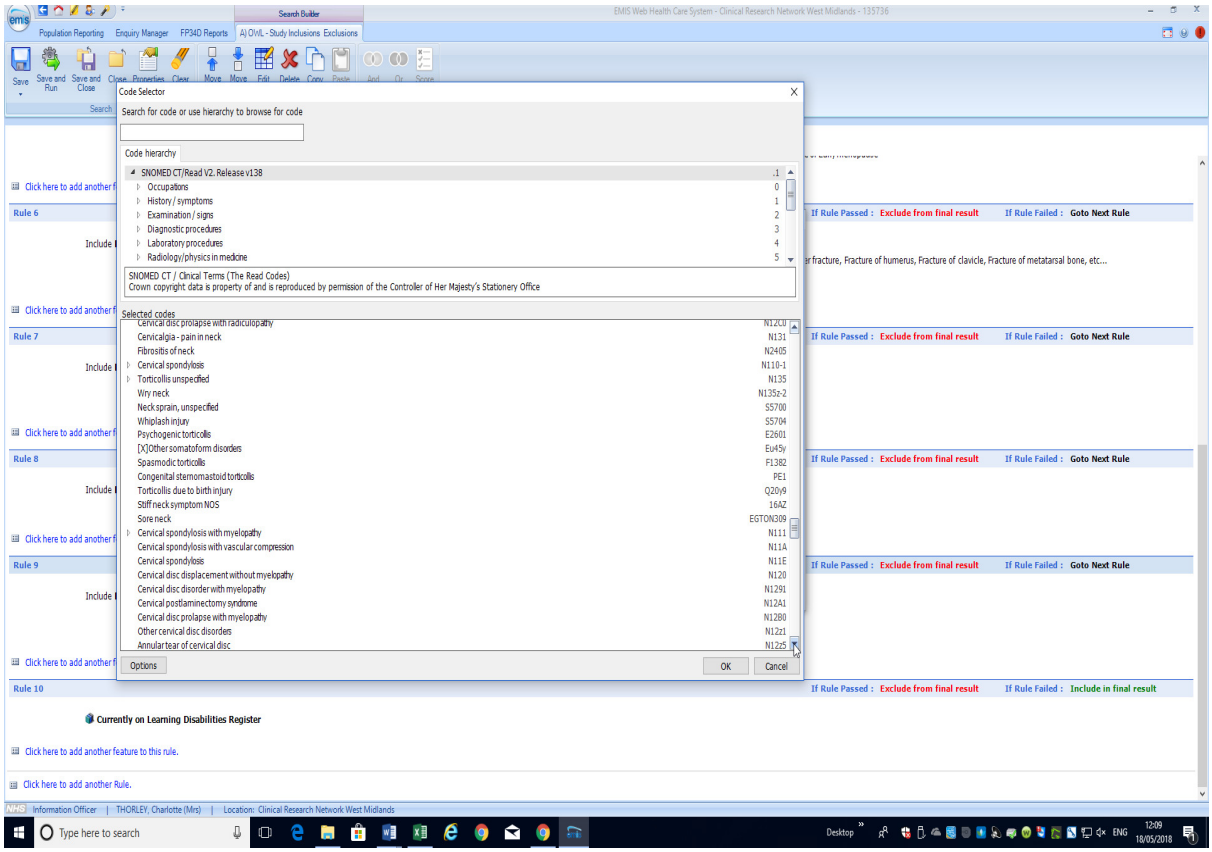
Selected codes
Arthralgia of other specified site N0948
Arthralgia of hip N094K
[D]Musculoskeletal pain R01z2
Polyarthropathy NEC N065-1
Arthritis N06z-1
Musculoskeletal pain - joints N096-2
[D]General aches and pains R00z2-1
Sero negative arthritis N04y1
Multiple stiff joints N0959
Walking difficulty due to multiple sites N0975
Joint disorder NOS, of multiple sites N09z9
Fibromyalgia N248
Soft tissue disorders NOS N24z
Arthropathy associated with mycoses, of multiple sites N016x
Other specified arthropathy of multiple sites N06y9
Chronic arthritis N06z8
Ankylosis of multiple joints N0859
Other specified joint disorders of multiple sites N09y9
Chronic osteomyelitis of multiple sites N3019
Stiff neck symptom Exclude some children 16A
Single-level cervical spondylosis without myelopathy N1100
Cervical spondylosis with radiculopathy N119
Cervical disc degeneration N125
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.
Type here to search


Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2. Release v138
Occupations
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Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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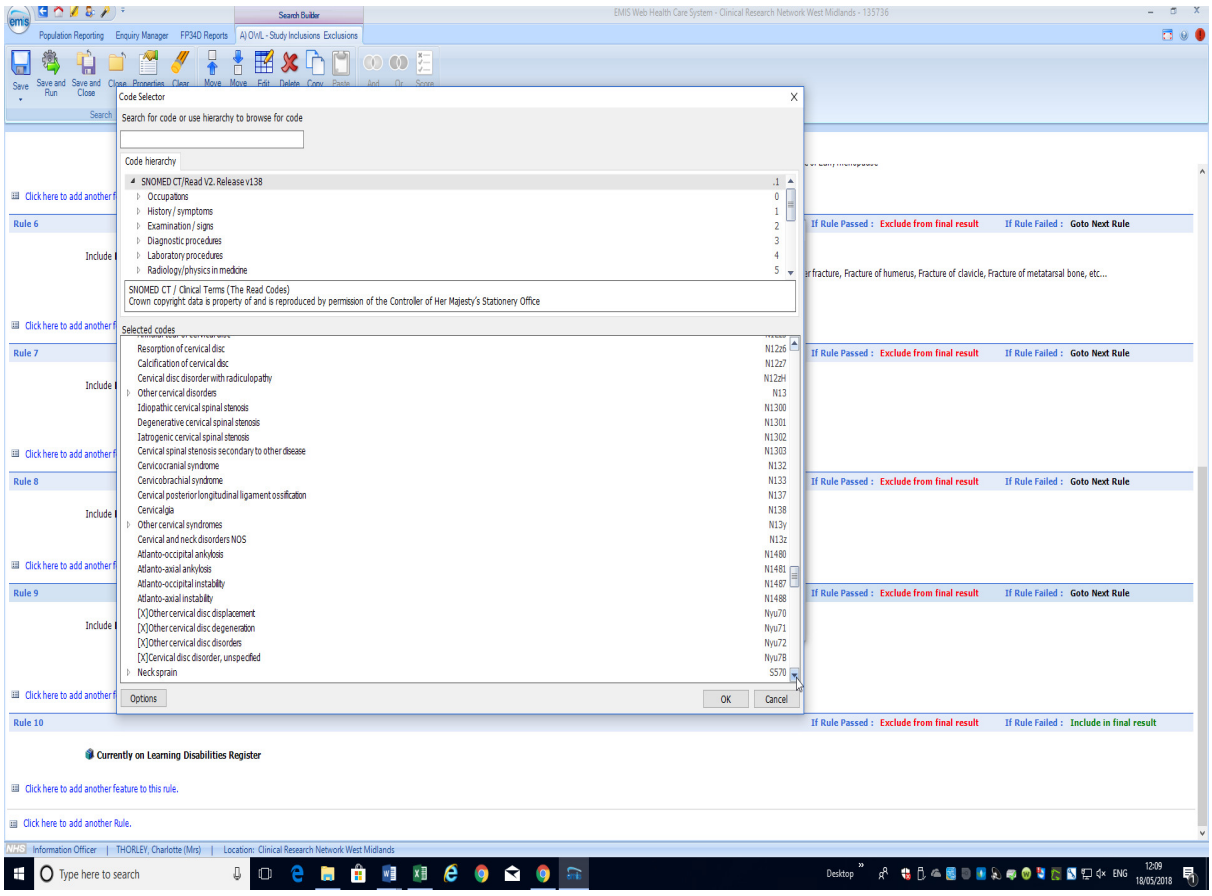
Selected codes
Cervicalgia - pain in neck
Fibrositis of neck
Cervical spondylosis
Torticollis unspecified
Wry neck
Neck sprain, unspecified
Whiplash injury
Psychogenic torticollis
[X]Other somatoform disorders
Spasmodic torticollis
Congenital sternomastoid torticollis
Torticollis due to birth injury
Stiff neck symptom NOS
Sore neck
Cervical spondylosis with myelopathy
Cervical spondylosis with vascular compression
Cervical spondylosis
Cervical disc displacement without myelopathy
Cervical disc disorder with myelopathy
Cervical postlaminectomy syndrome
Cervical disc prolapse with myelopathy
Other cervical disc disorders
Annular tear of cervical disc
Options
OK
Cancel
Currently on Learning Disabilities Register


Code Selector
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Code hierarchy
SNOMED CT/Read V2. Release v138
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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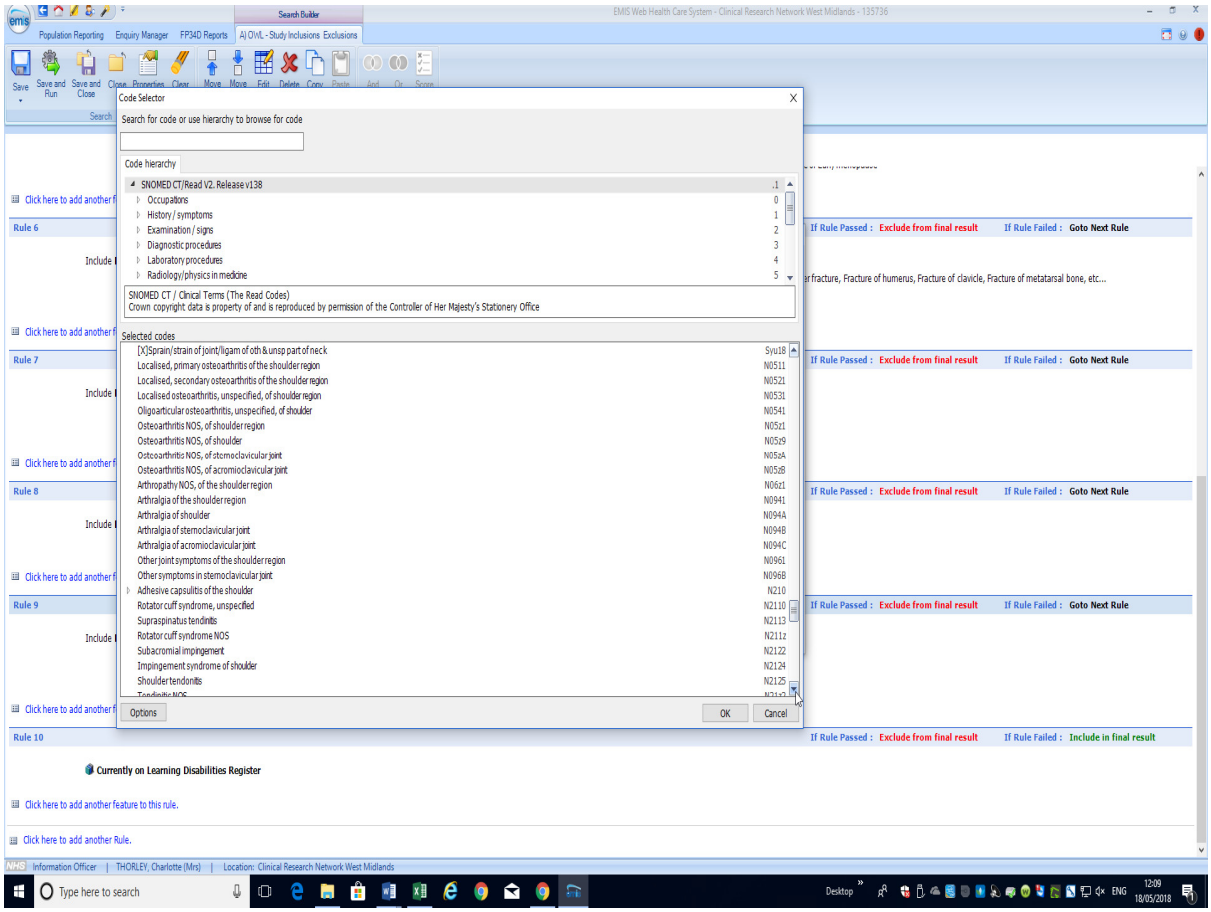
Selected codes
Resorption of cervical disc
Calcification of cervical disc
Cervical disc disorder with radiculopathy
Other cervical disorders
Idiopathic cervical spinal stenosis
Degenerative cervical spinal stenosis
Iatrogenic cervical spinal stenosis
Cervical spinal stenosis secondary to other disease
Cervicocranial syndrome
Cervicobrachial syndrome
Cervical posterior longitudinal ligament ossification
Cervicalgia
Other cervical syndromes
Cervical and neck disorders NOS
Atlanto-occipital ankylosis
Atlanto-axial ankylosis
Atlanto-occipital instability
Atlanto-axial instability
[X]Other cervical disc displacement
[X]Other cervical disc degeneration
[X]Other cervical disc disorders
[X]Cervical disc disorder, unspecified
Neck sprain
Options
OK
Cancel
Currently on Learning Disabilities Register


Code Selector
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Occupations
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Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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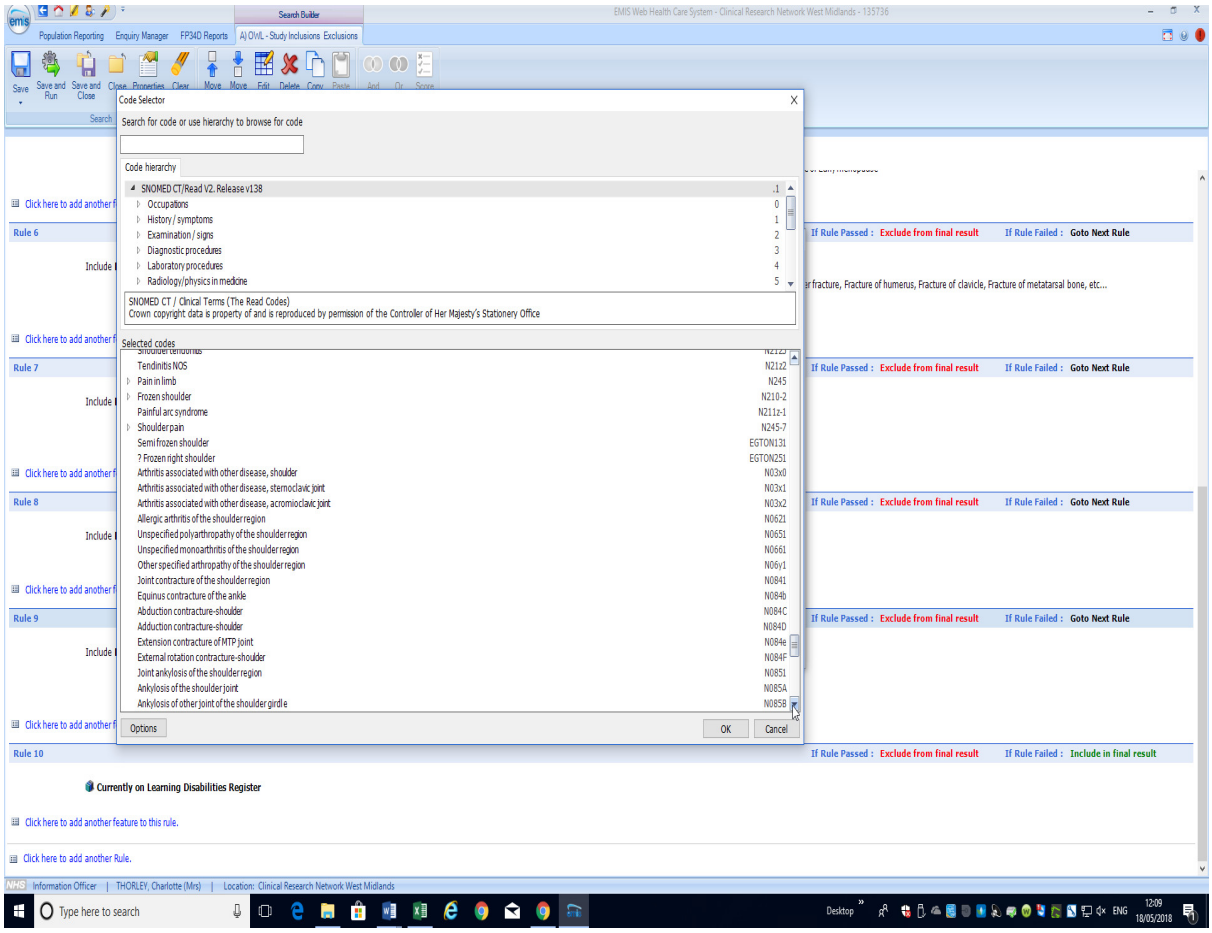
Selected codes
[X]Sprain/strain of joint/ligam of oth & unsp part of neck
Localised, primary osteoarthritis of the shoulder region
Localised, secondary osteoarthritis of the shoulder region
Localised osteoarthritis, unspecified, of shoulder region
Oligoarticular osteoarthritis, unspecified, of shoulder
Osteoarthritis NOS, of shoulder region
Osteoarthritis NOS, of shoulder
Osteoarthritis NOS, of sternoclavicular joint
Osteoarthritis NOS, of acromioclavicular joint
Arthropathy NOS, of the shoulder region
Arthralgia of the shoulder region
Arthralgia of shoulder
Arthralgia of sternoclavicular joint
Arthralgia of acromioclavicular joint
Other joint symptoms of the shoulder region
Other symptoms in sternoclavicular joint
Adhesive capsulitis of the shoulder
Rotator cuff syndrome, unspecified
Supraspinatus tendinitis
Rotator cuff syndrome NOS
Subacromial impingement
Impingement syndrome of shoulder
Shoulder tendonitis
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.


Code Selector
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Code hierarchy
SNOMED CT/Read V2. Release v138
Occupations
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Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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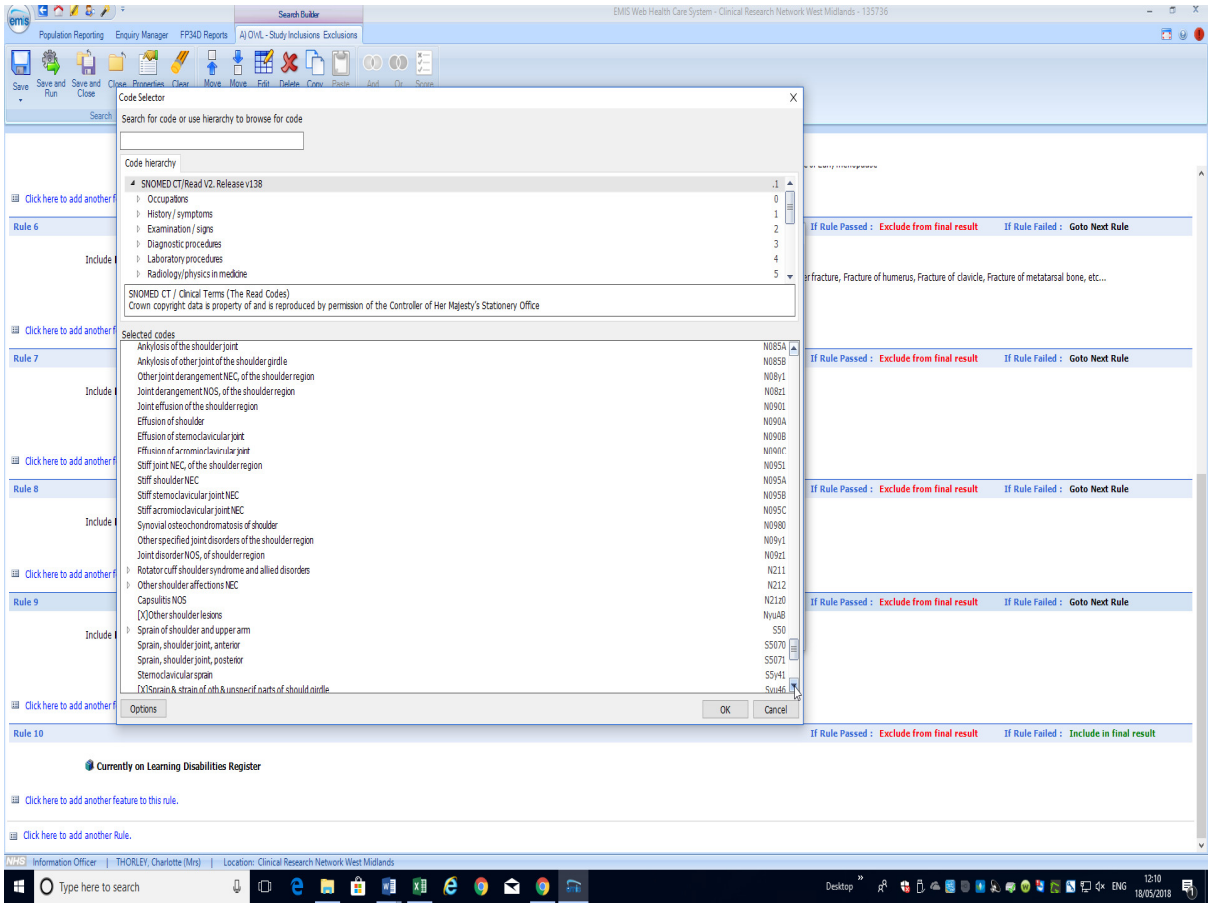
Selected codes
Tendinitis NOS N21z2
Pain in limb N245
Frozen shoulder N210-2
Painful arc syndrome N211z-1
Shoulder pain N245-7
Semi frozen shoulder EGTON131
? Frozen right shoulder EGTON251
Arthritis associated with other disease, shoulder N03x0
Arthritis associated with other disease, sternoclavic joint N03x1
Arthritis associated with other disease, acromioclavic joint N03x2
Allergic arthritis of the shoulder region N0621
Unspecified polyarthropathy of the shoulder region N0651
Unspecified monoarthritis of the shoulder region N0661
Other specified arthropathy of the shoulder region N06y1
Joint contracture of the shoulder region N0841
Equinus contracture of the ankle N084b
Abduction contracture-shoulder N084C
Adduction contracture-shoulder N084D
Extension contracture of MTP joint N084e
External rotation contracture-shoulder N084F
Joint ankylosis of the shoulder region N085J
Ankylosis of the shoulder joint N085A
Ankylosis of other joint of the shoulder girdle N085B
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.


Code Selector
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Selected codes
Ankylosis of the shoulder joint N085A
Ankylosis of other joint of the shoulder girdle N085B
Other joint derangement NEC, of the shoulder region N08y1
Joint derangement NOS, of the shoulder region N08z1
Joint effusion of the shoulder region N0901
Effusion of shoulder N090A
Effusion of sternoclavicular joint N090B
Stiff joint NEC, of the shoulder region N095I
Stiff shoulder NEC N095A
Stiff sternoclavicular joint NEC N095B
Stiff acromioclavicular joint NEC N095C
Synovial osteochondromatosis of shoulder N0980
Other specified joint disorders of the shoulder region N09y1
Joint disorder NOS, of shoulder region N09z1
Rotator cuff shoulder syndrome and allied disorders N211
Other shoulder affections NEC N212
Capsulitis NOS N21z0
[X]Other shoulder lesions NyuAB
Sprain of shoulder and upper arm S50
Sprain, shoulder joint, anterior S5070
Sprain, shoulder joint, posterior S5071
Sternoclavicular sprain S5y41
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
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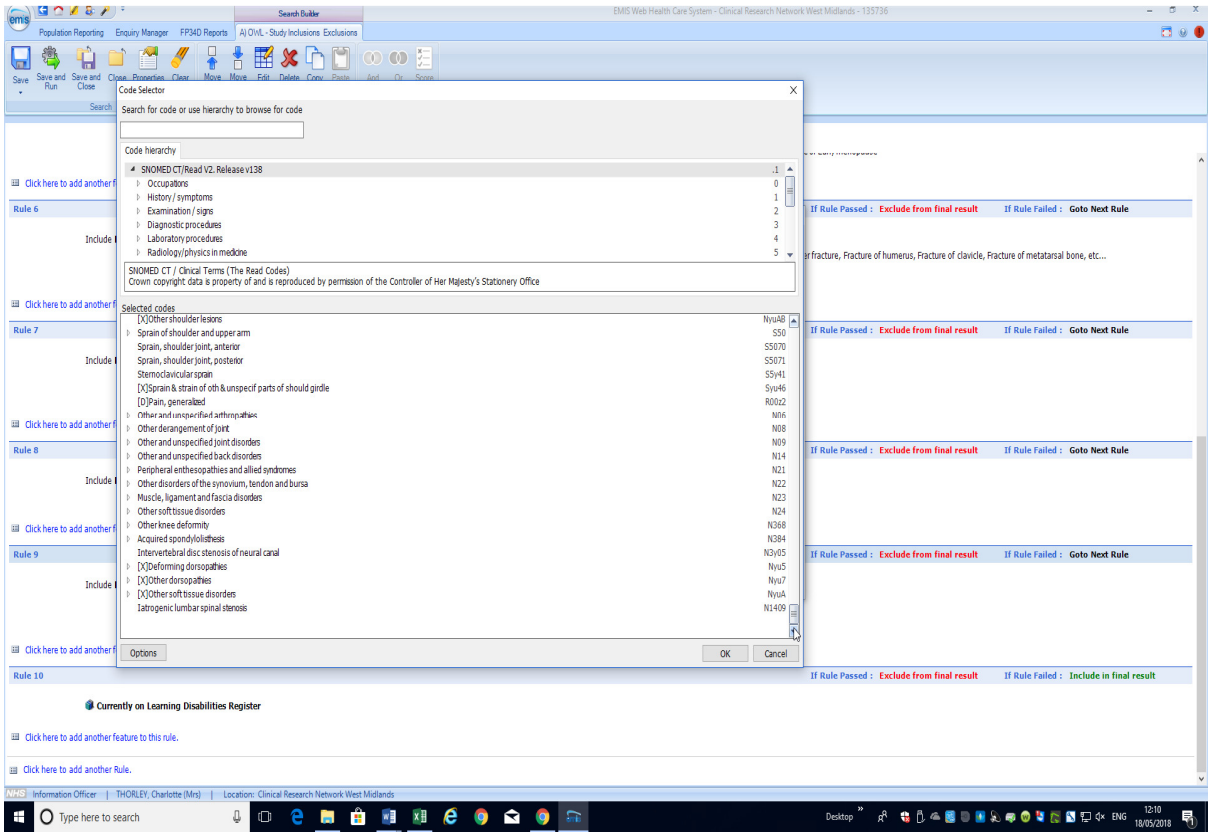
Code Selector
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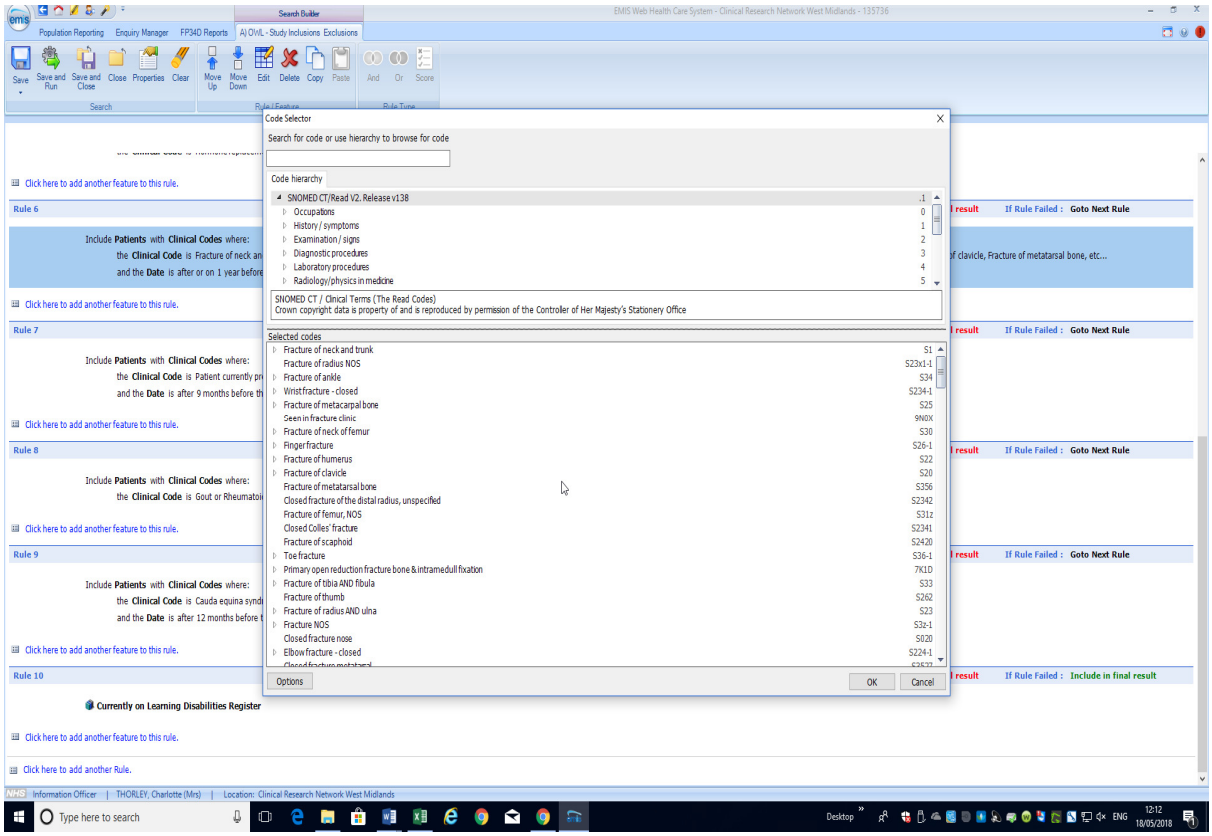
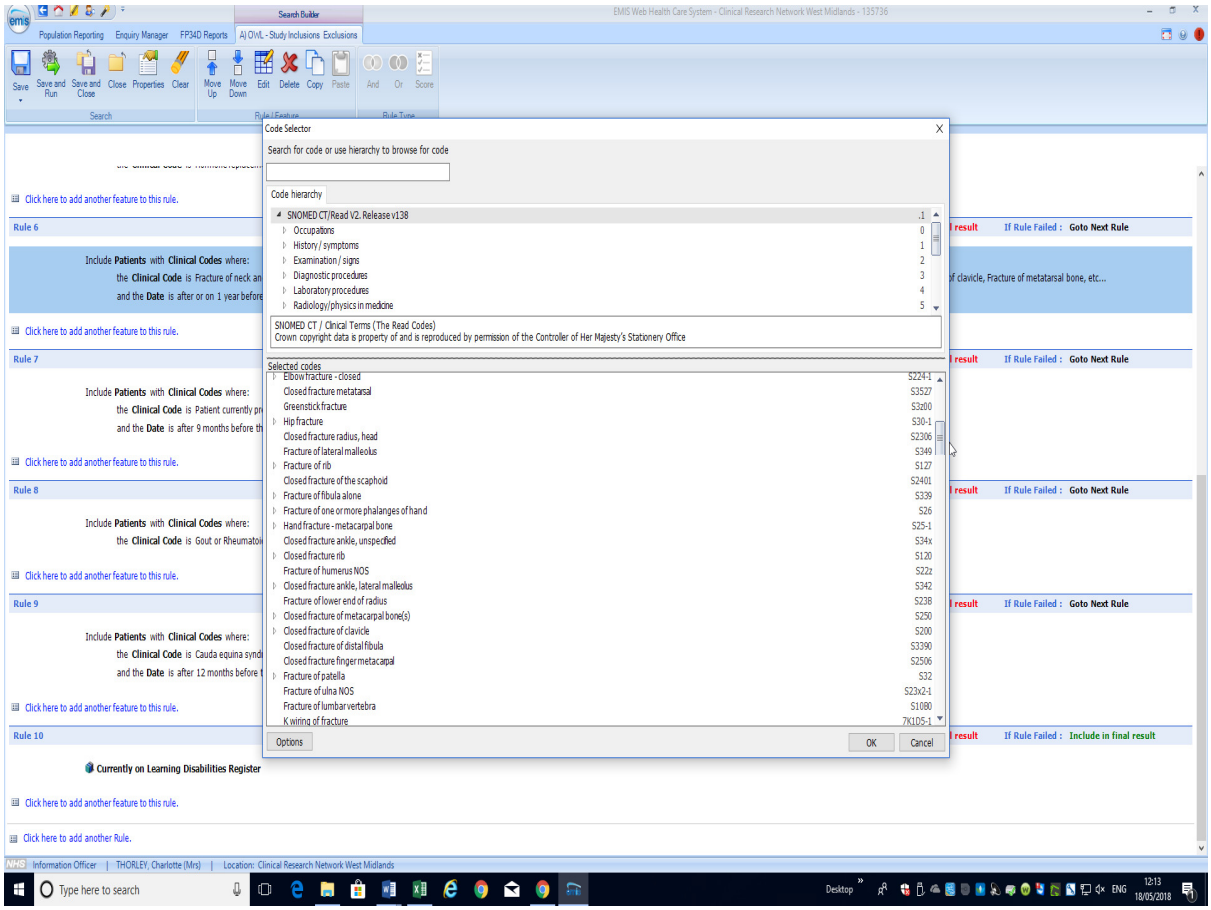
Selected codes
[X]Other shoulder lesions NyuAB
Sprain of shoulder and upper arm S50
Sprain, shoulder joint, anterior S5070
Sprain, shoulder joint, posterior S5071
Sternoclavicular sprain S5y41
[X]Sprain & strain of oth & unspecif parts of should girdle Syu46
[D]Pain, generalized R00z2
Other derangement of joint N08
Other and unspecified joint disorders N09
Other and unspecified back disorders N14
Peripheral enthesopathies and allied syndromes N21
Other disorders of the synovium, tendon and bursa N22
Muscle, ligament and fascia disorders N23
Other soft tissue disorders N24
Other knee deformity N368
Acquired spondylolisthesis N384
Intervertebral disc stenosis of neural canal N3y05
[X]Deforming dorsopathies Nyu5
[X]Other dorsopathies Nyu7
[X]Other soft tissue disorders NyuA
Iatrogenic lumbar spinal stenosis N1409
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.

Exclusions Criteria




Code Selector
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Code hierarchy
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Occupations
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Examination / signs
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Radiology/physics in medicine
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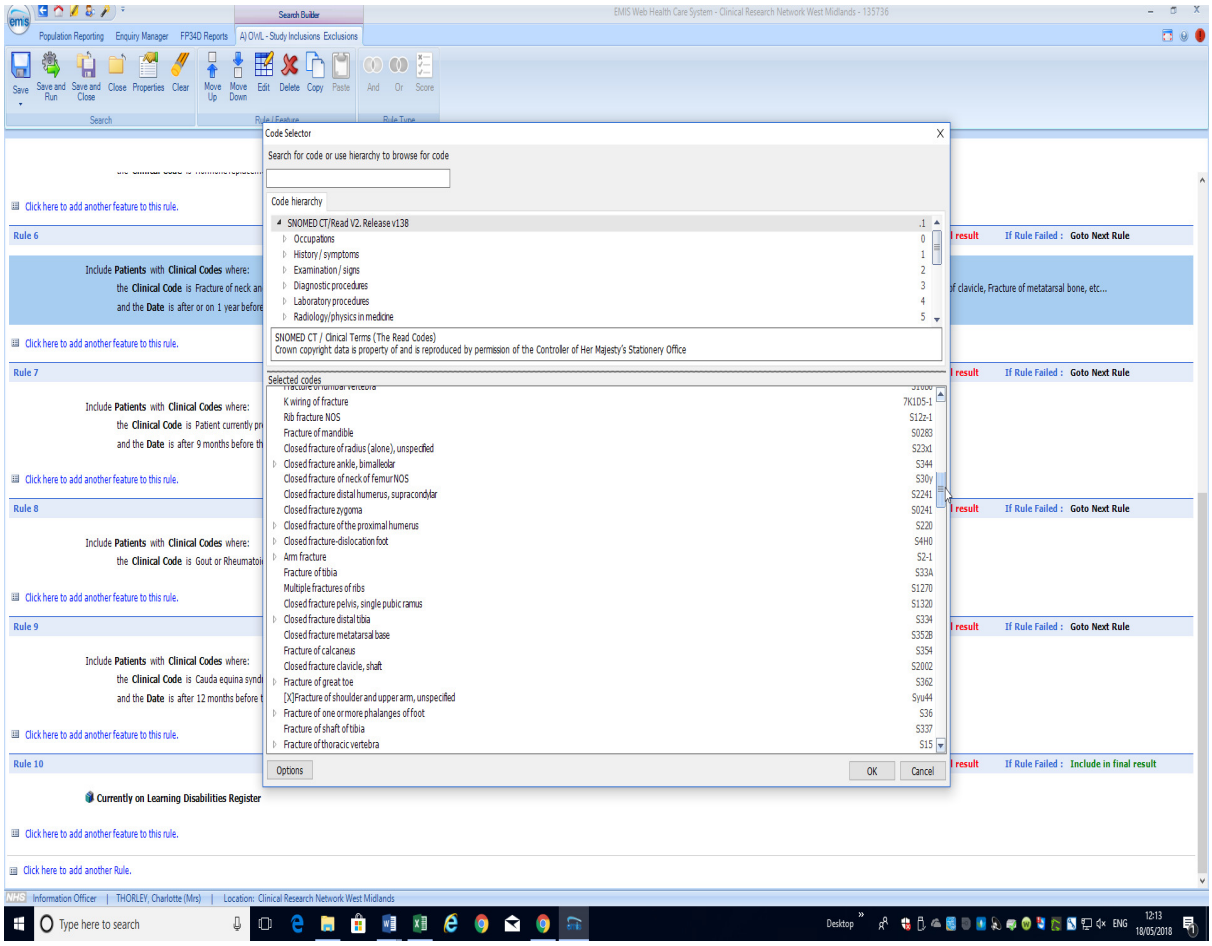
Selected codes
Elbow fracture - closed
Closed fracture metatarsal
Greenstick fracture
Hip fracture
Closed fracture radius, head
Fracture of lateral malleolus
Fracture of rib
Closed fracture of the scaphoid
Fracture of fibula alone
Fracture of one or more phalanges of hand
Hand fracture - metacarpal bone
Closed fracture ankle, unspecified
Closed fracture rib
Fracture of humerus NOS
Closed fracture ankle, lateral malleolus
Fracture of lower end of radius
Closed fracture of metacarpal bone(s)
Closed fracture of clavicle
Closed fracture of distal fibula
Closed fracture finger metacarpal
Fracture of patella
Fracture of ulna NOS
Fracture of lumbar vertebra
K wiring of fracture
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
Currently on Learning Disabilities Register
Click here to add another Rule.


Search Builder
Population Reporting
Enquiry Manager
FP34D Reports
A) OWL - Study Inclusions Exclusions
Save
Save and Run
Save and Close
Close
Properties
Clear
Move Up
Move Down
Edit
Delete
Copy
Paste
And
Or
Score
Search
Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
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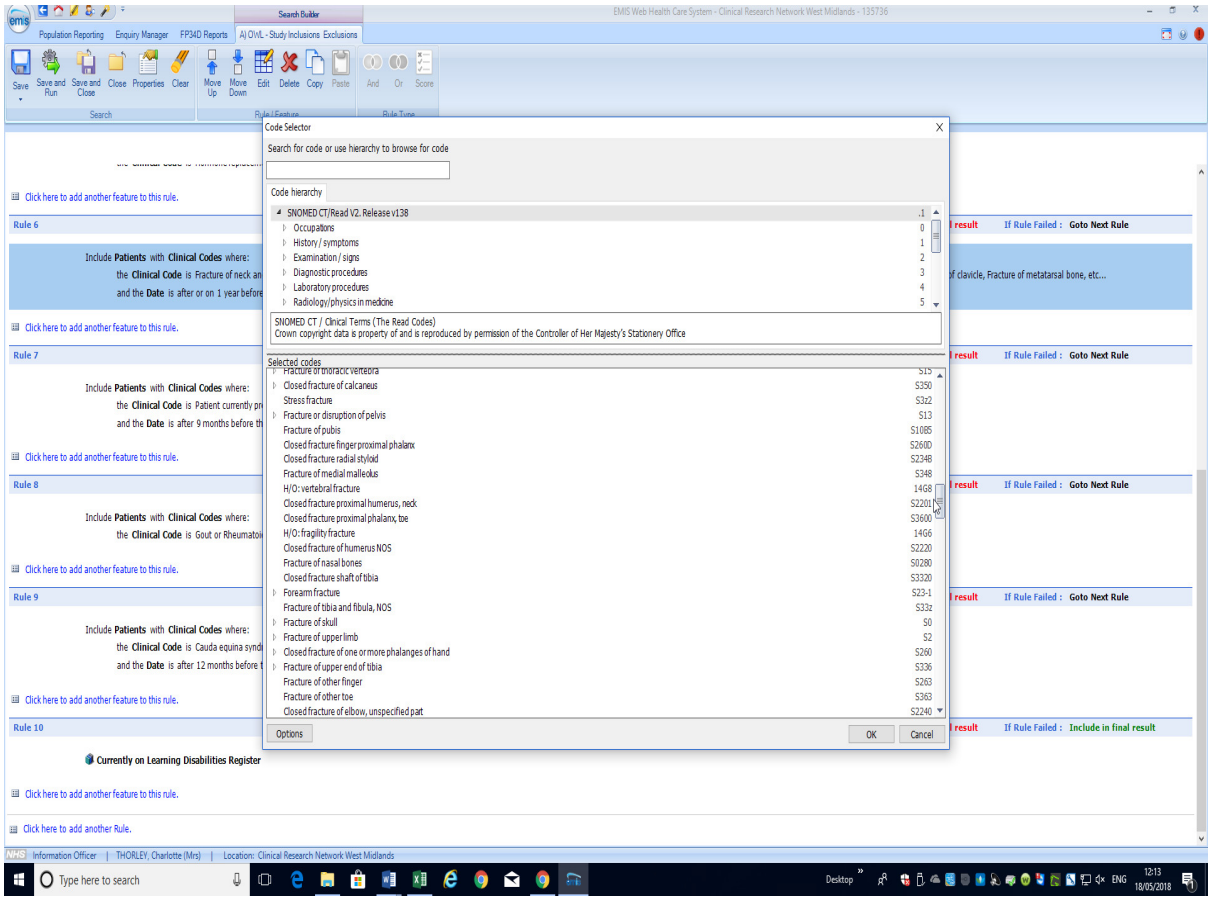
Selected codes
K wiring of fracture
Rib fracture NOS
Fracture of mandible
Closed fracture of radius (alone), unspecified
Closed fracture ankle, bimalleolar
Closed fracture of neck of femur NOS
Closed fracture distal humerus, supracondylar
Closed fracture zygoma
Closed fracture of the proximal humerus
Closed fracture-dislocation foot
Arm fracture
Fracture of tibia
Multiple fractures of ribs
Closed fracture pelvis, single pubic ramus
Closed fracture distal tibia
Closed fracture metatarsal base
Fracture of calcaneus
Closed fracture clavicle, shaft
Fracture of great toe
[X]Fracture of shoulder and upper arm, unspecified
Fracture of one or more phalanges of foot
Fracture of shaft of tibia
Fracture of thoracic vertebra
Options
OK
Cancel
Click here to add another feature to this rule.
Rule 6
Include Patients with Clinical Codes where:
the Clinical Code is Fracture of neck an
and the Date is after or on 1 year before
Rule 7
Include Patients with Clinical Codes where:
the Clinical Code is Patient currently pr
and the Date is after 9 months before th
Rule 8
Include Patients with Clinical Codes where:
the Clinical Code is Gout or Rheumatoi
Rule 9
Include Patients with Clinical Codes where:
the Clinical Code is Cauda equina syndr
and the Date is after 12 months before t
Rule 10
Currently on Learning Disabilities Register
Click here to add another Rule.
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Information Officer | THORLEY, Charlotte (Mrs) | Location: Clinical Research Network West Midlands
Type here to search
Desktop
ENG
12:13
18/05/2018


Search Builder
Population Reporting
Enquiry Manager
FP34D Reports
AJ OWL - Study Inclusions Exclusions
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Search
Rule / Feature
Rule Type
Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2. Release v138
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
Crown copyright data is property of and is reproduced by permission of the Controller of Her Majesty's Stationery Office
Selected codes
Closed fracture of calcaneus
Stress fracture
Fracture or disruption of pelvis
Fracture of pubis
Closed fracture finger proximal phalanx
Closed fracture radial styloid
Fracture of medial malleolus
H/O: vertebral fracture
Closed fracture proximal humerus, neck
Closed fracture proximal phalanx, toe
H/O: fragility fracture
Closed fracture of humerus NOS
Fracture of nasal bones
Closed fracture shaft of tibia
Forearm fracture
Fracture of tibia and fibula, NOS
Fracture of skull
Fracture of upper limb
Closed fracture of one or more phalanges of hand
Fracture of upper end of tibia
Fracture of other finger
Fracture of other toe
Closed fracture of elbow, unspecified part
Options
OK
Cancel
Click here to add another feature to this rule.
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
Currently on Learning Disabilities Register
Click here to add another Rule.
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Information Officer | THORLEY, Charlotte (Mrs) | Location: Clinical Research Network West Midlands
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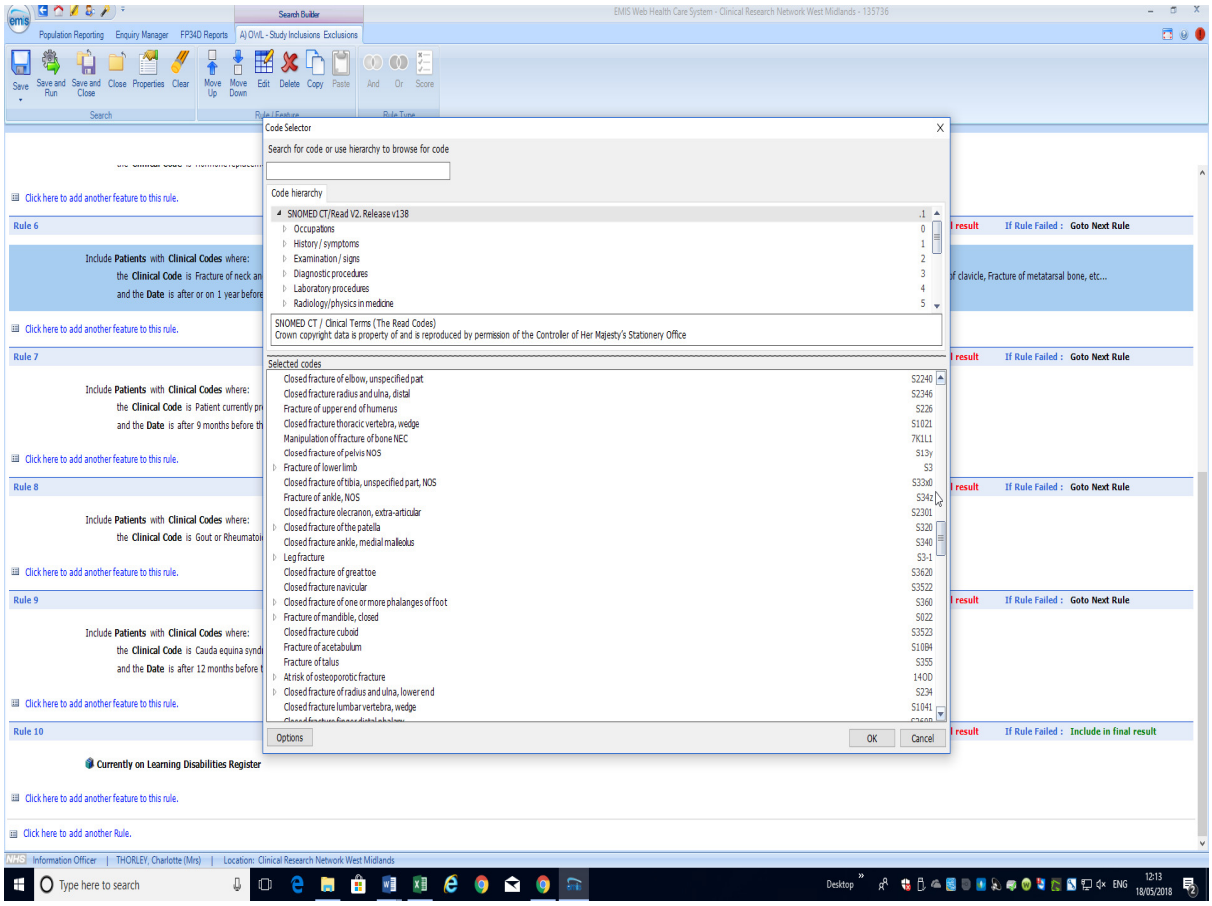
18/05/2018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History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
Crown copyright data is property of and is reproduced by permission of the Controller of Her Majesty's Stationery Office
Selected codes
Closed fracture of elbow, unspecified part S2240
Closed fracture radius and ulna, distal S2346
Fracture of upper end of humerus S226
Closed fracture thoracic vertebra, wedge S1021
Manipulation of fracture of bone NEC 7K1L1
Closed fracture of pelvis NOS S13y
Fracture of lower limb S3
Closed fracture of tibia, unspecified part, NOS S33x0
Fracture of ankle, NOS S34z
Closed fracture olecranon, extra-articular S2301
Closed fracture of the patella S320
Closed fracture ankle, medial malleolus S340
Leg fracture S3-1
Closed fracture of great toe S3620
Closed fracture navicular S3522
Closed fracture of one or more phalanges of foot S360
Fracture of mandible, closed S022
Closed fracture cuboid S3523
Fracture of acetabulum S10B4
Fracture of talus S355
Atrisk of osteoporotic fracture 140D
Closed fracture of radius and ulna, lower end S234
Closed fracture lumbar vertebra, wedge S1041
Options
OK
Cancel
Click here to add another feature to this rule.
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
Currently on Learning Disabilities Register
Click here to add another Rule.
Information Officer | THORLEY, Charlotte (Mrs) | Location: Clinical Research Network West Midlands
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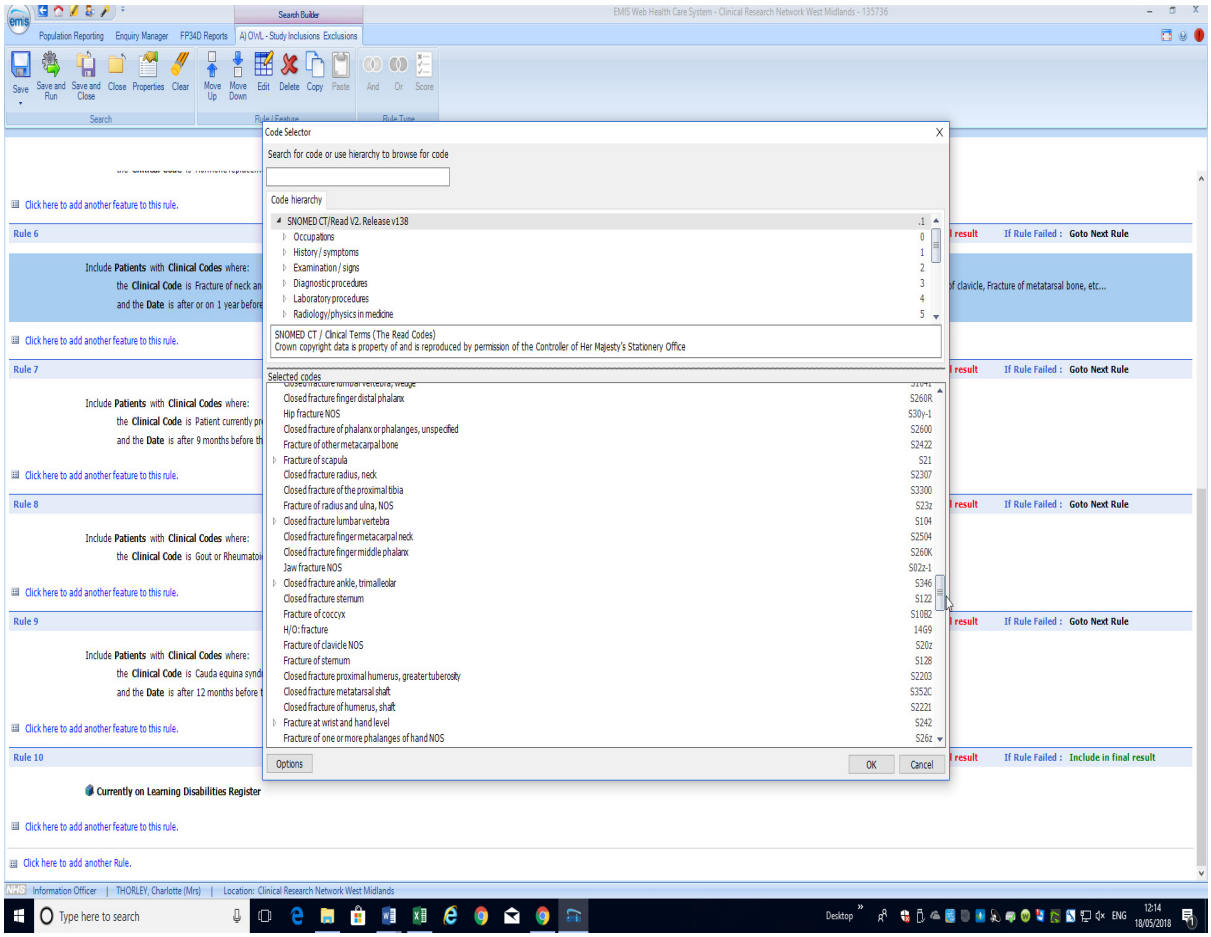
18/05/2018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Enquiry Manager
FP34D Reports
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Code hierarchy
SNOMED CT/Read V2. Release v138
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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Selected codes
Closed fracture finger distal phalanx
Hip fracture NOS
Closed fracture of phalanx or phalanges, unspecified
Fracture of other metacarpal bone
Fracture of scapula
Closed fracture radius, neck
Closed fracture of the proximal tibia
Fracture of radius and ulna, NOS
Closed fracture lumbar vertebra
Closed fracture finger metacarpal neck
Closed fracture finger middle phalanx
Jaw fracture NOS
Closed fracture ankle, trimalleolar
Closed fracture sternum
Fracture of coccyx
H/O: fracture
Fracture of clavicle NOS
Fracture of sternum
Closed fracture proximal humerus, greater tuberosity
Closed fracture metatarsal shaft
Closed fracture of humerus, shaft
Fracture at wrist and hand level
Fracture of one or more phalanges of hand NOS
Options
OK
Cancel
Click here to add another feature to this rule.
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
Currently on Learning Disabilities Register
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Information Officer | THORLEY, Charlotte (Mrs) | Location: Clinical Research Network West Midlands
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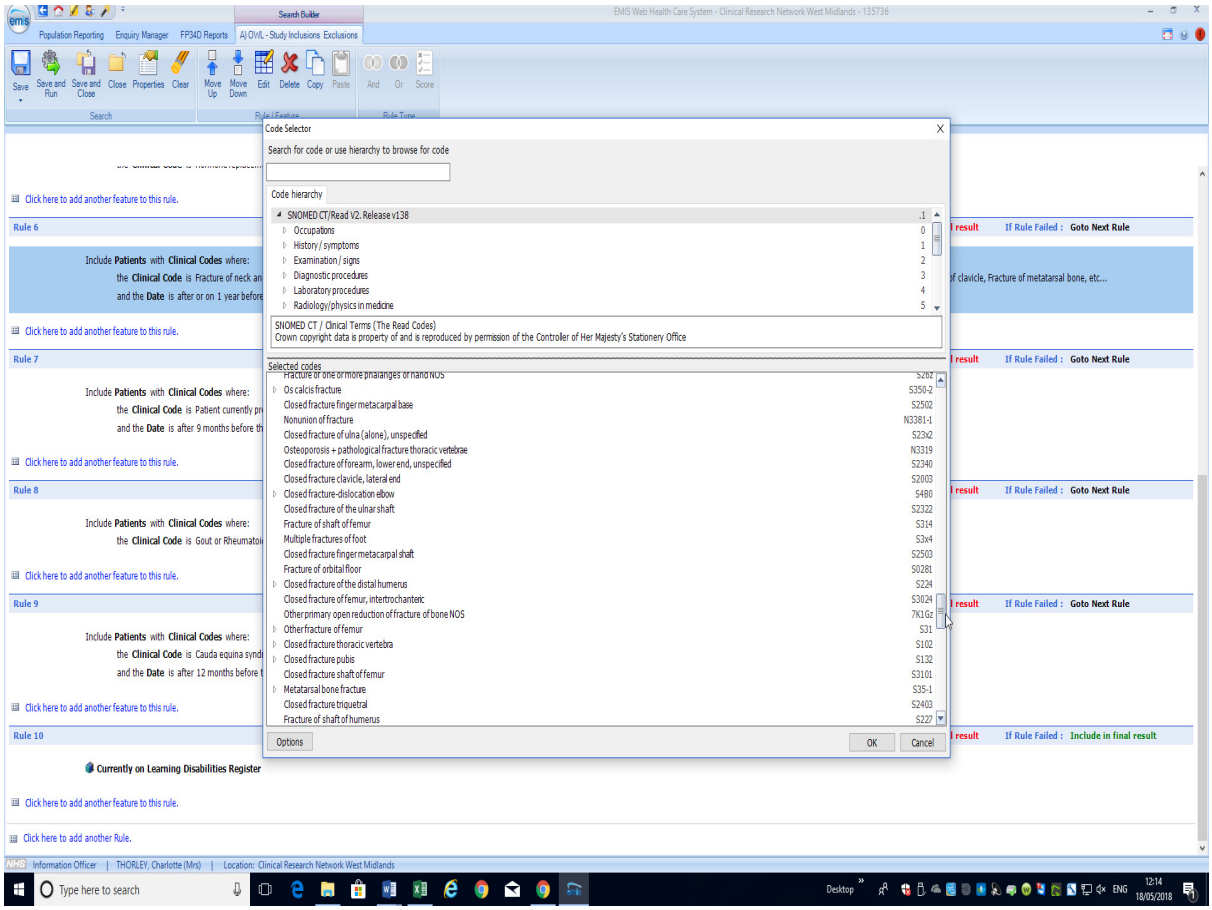
18/05/2018


Search Builder
Population Reporting
Enquiry Manager
FP34D Reports
AJ OWL - Study Inclusions Exclusions
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Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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Selected codes
Os calcis fracture
Closed fracture finger metacarpal base
Nonunion of fracture
Closed fracture of ulna (alone), unspecified
Osteoporosis + pathological fracture thoracic vertebrae
Closed fracture of forearm, lower end, unspecified
Closed fracture clavicle, lateral end
Closed fracture-dislocation elbow
Closed fracture of the ulnar shaft
Fracture of shaft of femur
Multiple fractures of foot
Closed fracture finger metacarpal shaft
Fracture of orbital floor
Closed fracture of the distal humerus
Closed fracture of femur, intertrochanteric
Other primary open reduction of fracture of bone NOS
Other fracture of femur
Closed fracture thoracic vertebra
Closed fracture pubis
Closed fracture shaft of femur
Metatarsal bone fracture
Closed fracture triquetral
Fracture of shaft of humerus
Options
OK
Cancel
Rule 6
Rule 7
Rule 8
Rule 9
Rule 10
Currently on Learning Disabilities Register
Click here to add another feature to this rule.
Click here to add another Rule.
If Rule Failed : Goto Next Rule
If Rule Failed : Include in final result
Information Officer | THORLEY, Charlotte (Mrs) | Location: Clinical Research Network West Midlands
Type here to search
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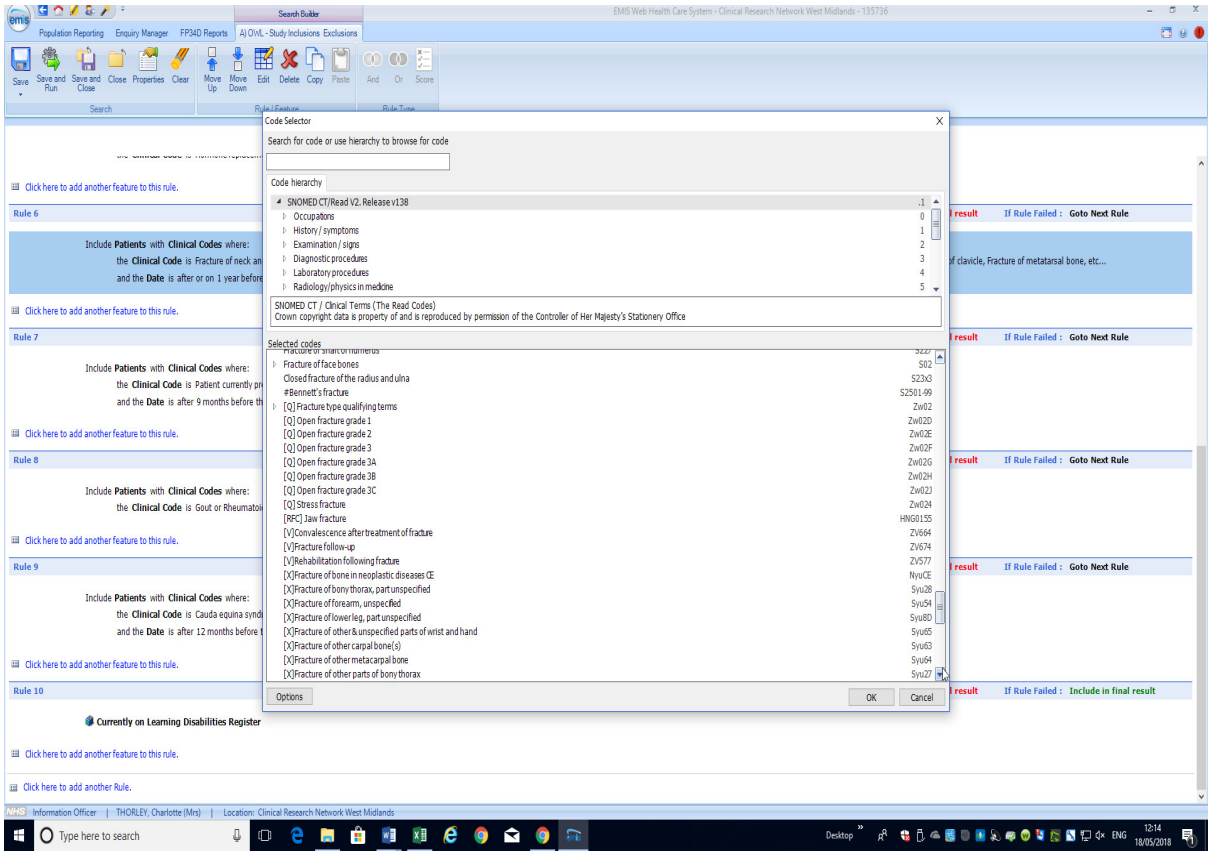
18/05/2018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Code hierarchy
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Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
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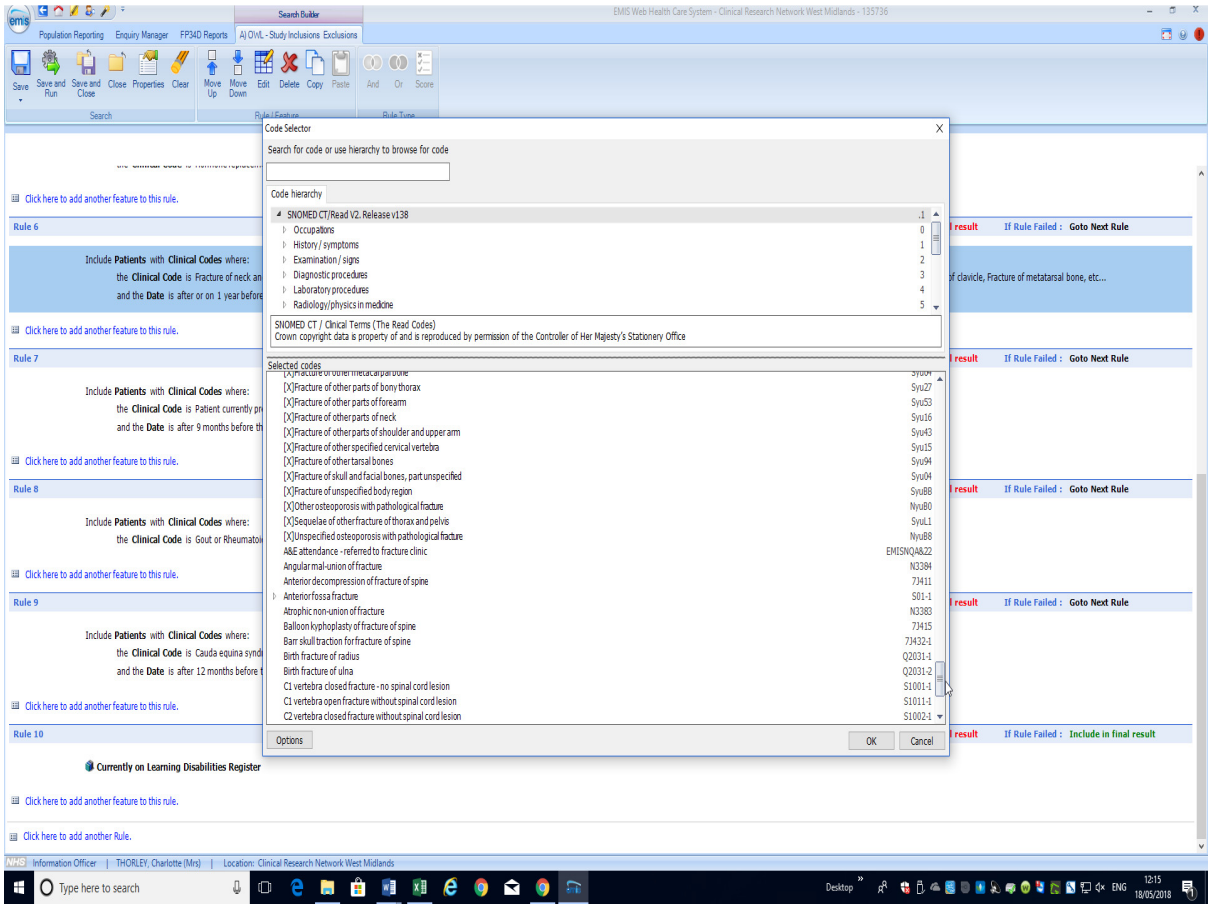
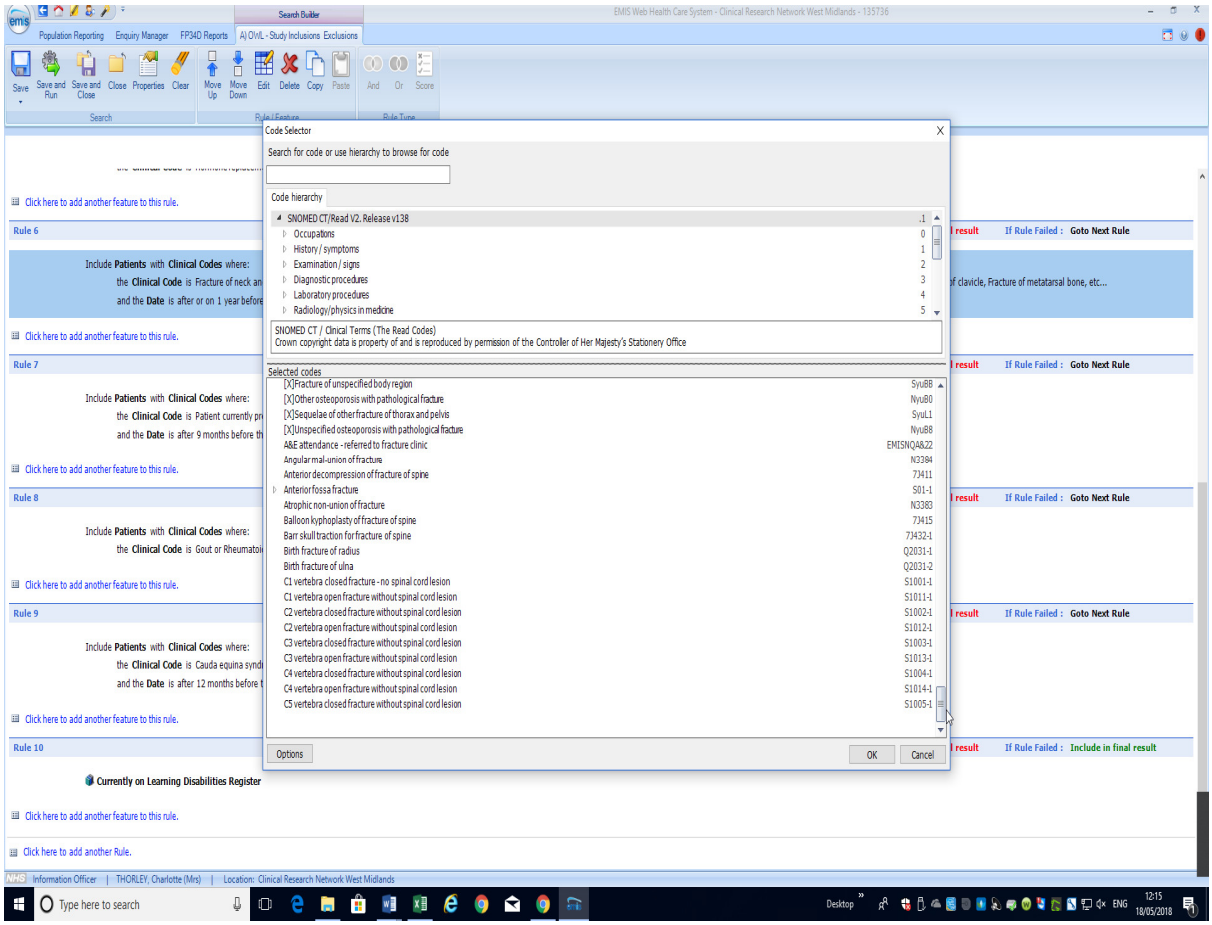
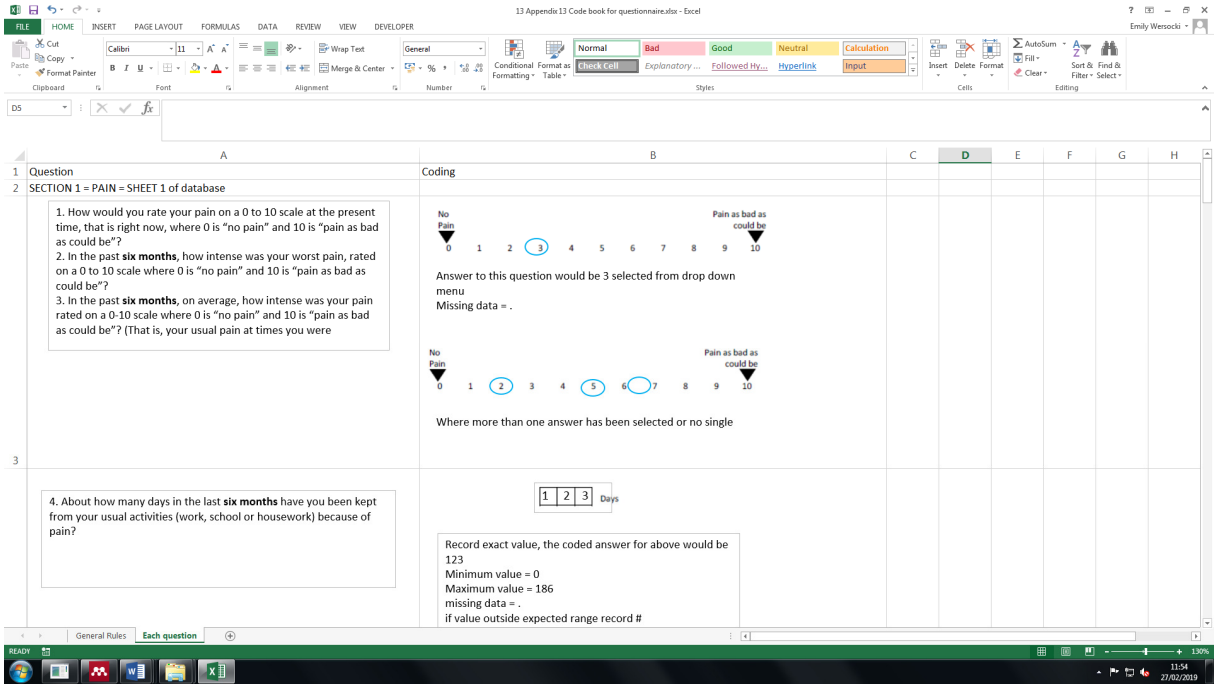
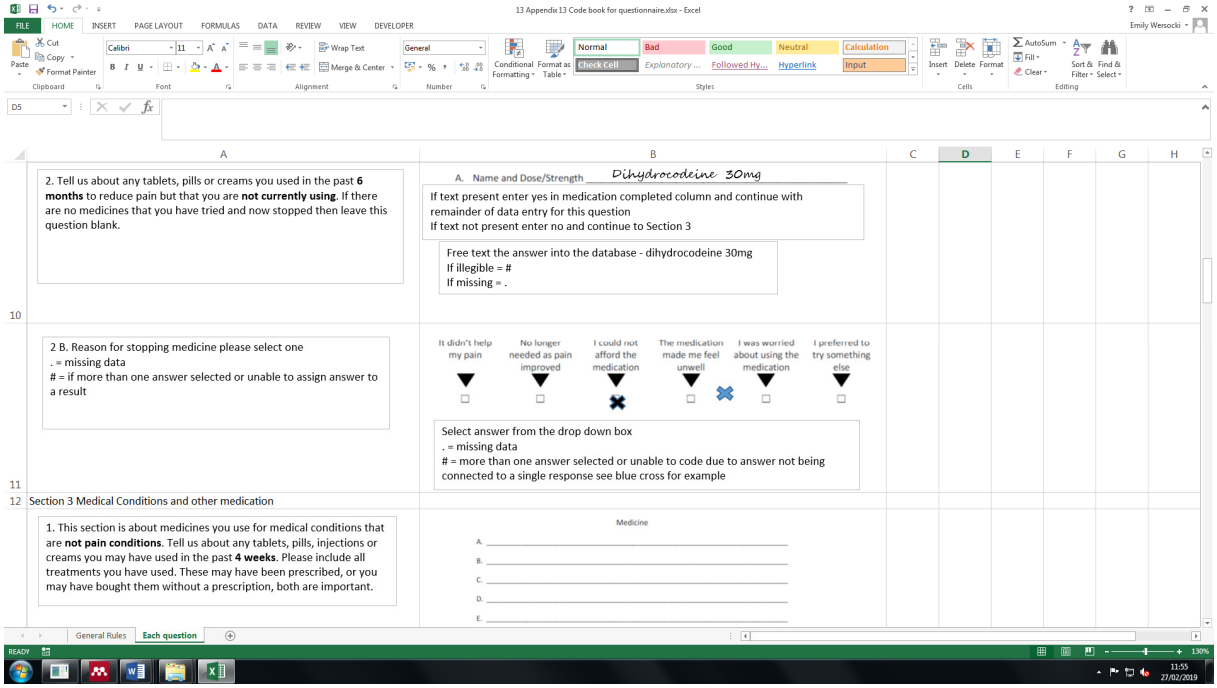
Selected codes
Fracture of face bones
Closed fracture of the radius and ulna
#Bennett's fracture
[Q] Fracture type qualifying terms
[Q] Open fracture grade 1
[Q] Open fracture grade 2
[Q] Open fracture grade 3
[Q] Open fracture grade 3A
[Q] Open fracture grade 3B
[Q] Open fracture grade 3C
[Q] Stress fracture
[RFC] Jaw fracture
[V] Convalescence after treatment of fracture
[V] Fracture follow-up
[V] Rehabilitation following fracture
[X] Fracture of bone in neoplastic diseases
[X] Fracture of bony thorax, part unspecified
[X] Fracture of forearm, unspecified
[X] Fracture of lower leg, part unspecified
[X] Fracture of other & unspecified parts of wrist and hand
[X] Fracture of other carpal bone(s)
[X] Fracture of other metacarpal bone
[X] Fracture of other parts of bony thorax
Options
OK
Cancel
Currently on Learning Disabilities Register


Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2. Release v138
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
Crown copyright data is property of and is reproduced by permission of the Controller of Her Majesty's Stationery Office
Selected codes
[X] Fracture of other parts of bony thorax
[X] Fracture of other parts of forearm
[X] Fracture of other parts of neck
[X] Fracture of other parts of shoulder and upper arm
[X] Fracture of other specified cervical vertebra
[X] Fracture of other tarsal bones
[X] Fracture of skull and facial bones, part unspecified
[X] Fracture of unspecified body region
[X] Other osteoporosis with pathological fracture
[X] Sequelae of other fracture of thorax and pelvis
[X] Unspecified osteoporosis with pathological fracture
A&E attendance - referred to fracture clinic
Angular mal-union of fracture
Anterior decompression of fracture of spine
Anterior fossa fracture
Atrophic non-union of fracture
Balloon kyphoplasty of fracture of spine
Barr skull traction for fracture of spine
Birth fracture of radius
Birth fracture of ulna
C1 vertebra closed fracture - no spinal cord lesion
C1 vertebra open fracture without spinal cord lesion
C2 vertebra closed fracture without spinal cord lesion
Options
OK
Cancel
Currently on Learning Disabilities Register


Code Selector
Search for code or use hierarchy to browse for code
Code hierarchy
SNOMED CT/Read V2, Release v138
Occupations
History / symptoms
Examination / signs
Diagnostic procedures
Laboratory procedures
Radiology/physics in medicine
SNOMED CT / Clinical Terms (The Read Codes)
Crown copyright data is property of and is reproduced by permission of the Controller of Her Majesty's Stationery Office
Selected codes
[X]Fracture of unspecified body region
[X]Other osteoporosis with pathological fracture
[X]Sequelae of other fracture of thorax and pelvis
[X]Unspecified osteoporosis with pathological fracture
A&E attendance - referred to fracture clinic
Angular mal-union of fracture
Anterior decompression of fracture of spine
Anterior fossa fracture
Atrophic non-union of fracture
Balloon kyphoplasty of fracture of spine
Barr skull traction for fracture of spine
Birth fracture of radius
Birth fracture of ulna
C1 vertebra closed fracture - no spinal cord lesion
C1 vertebra open fracture without spinal cord lesion
C2 vertebra closed fracture without spinal cord lesion
C2 vertebra open fracture without spinal cord lesion
C3 vertebra closed fracture without spinal cord lesion
C3 vertebra open fracture without spinal cord lesion
C4 vertebra closed fracture without spinal cord lesion
C4 vertebra open fracture without spinal cord lesion
C5 vertebra closed fracture without spinal cord lesion
Options
OK
Cancel
Currently on Learning Disabilities Register

Appendix 13: Screenshot of code book for data input from paper questionnaires





Appendix 14: SF-12 student license agreement

Keele UNIVERSITY

Emily Richardson <e.wersocki@keele.ac.uk>

SF-12v2 FREE STUDENT LICENSE AGREEMENT QM039359 – OPTUM #CT184958 OP059432

Lynda LaPlante <llaplante@qualitymetric.com> 16 February 2017 at 15:19
To: "e.wersocki@keele.ac.uk" <e.wersocki@keele.ac.uk>

Dear Emily,

Below please find your license agreement with $0.00 invoice for the Health Survey under the Unfunded Student Program. Under this program, the survey with reference and scoring materials will be provided to you at no charge at all.

This license is limited to your thesis/dissertation only. The survey, data and/or research finding are not to be used for any other purpose. Your customer number is **CT184958** and your ID # for this thesis/dissertation project is **OP059432**. Please use these numbers in any communication with us.

UNDERSTANDING YOUR LICENSE:

Your Data Collection, Scoring & Interpretation License Package includes:

- Access to the SF-12v2® 4-week recall survey in 1 language – United Kingdom (English)
- Permission provided only for project listed in license agreement under **Approved Purpose** on page 1. Permission is not transferrable for any purpose other than student's thesis or to any other project.
- License Start and End Date: 01-September 2017 to 31-December 2017
- Survey Administration Method: self administration via paper/pencil
- Maximum of 1,000 survey administrations
- SF-12v2 E-Manual - US (English)
- Certified Scoring Software 5.0™ (for batch scoring using desktop scoring application)
- Maximum of 1,000 scoring credits for the SF-12v2®
- Includes scoring features of MDE (Maximum Data Recovery), DQE (Data Quality Evaluation w/ report) and UI (Utility Index QALYs)
- **Expiration Date: This pricing expires in 30 days, on the 16-March 2017.** Please sign and return the attached license agreement before this date to secure pricing. If there is a reason why you will not be able to finalize your license within 30 days, please contact me at llaplante@qualitymetric.com for an extension.
- **Please do not use any survey forms that you have access to. We will provide you wih a new set to ensure you are using the most current, validated questionnaire.**

Important Scoring Software 5.0™ Information:

The scoring software is required to score and understand your data. This requirement has been put into place due to a large amount of errors incurred from hand scored data that have comprised study outcomes. The Scoring Software is a desktop application that is good for one download. There are **3 ways to enter your data into the software**: importing, data entry or entering survey responses on simulated survey form. Once scored, you do have the option of downloading the scored data into SPSS, SAS or the analytical software of your choice for further analysis.

We provide you with a "Software Key" which is the activation code to use the Scoring Software. This key is pre-loaded with the scoring credits needed for your specific survey/study and will expire when the credits are used.

- Summary of important facts about the software:
  - ✓ Download link and Activation Key are valid for one download on one computer only - if second copy is required, contact sales representative llaplante@qualitymetric.com
  - ✓ Software is **NOT** compatiable with MAC computers.
  - ✓ Usage cannot be transferred to another computer once downloaded

- ✓ There is no timelimit on the software
- ✓ You will receive an Activation Key that is pre-loaded with the scoring credits needed for this specific project. This key can not be used for any other projects. It will expire when the pre-loaded scoring credits are used. Your order is scheduled to be pre-loaded with **1,000** scoring credits for the **SF-12v2®** Health Survey. The number of scoring credits is based upon the number of survey administrations are to be licensed for under this project.
- ✓ Once a data record is entered, a scoring credit is deducted from the overall total of **1,000** and can not be reset. (Please NOTE: If you enter test data or edit and re-enter data or enter a bad record, this also is considered a data record by the software and a scoring credit will be deducted from the overall total.)
- ✓ If you run out of credits, please contact sales representative llaplante@qualitymetric.com.

Important Note: This version includes the NEW 2009 U.S. General Population Norms in addition to the 1998 U.S. General Population Norms. If you have already begun to score your data or if this research is a continuation of a longitudinal study, you must continue to use the norms you have begun scoring with. You can not co-mingle data scored with different norms and achieve valid and reliable results. In these cases, if you wanted to switch to the 2009 norms you would have to re-score all of your previously scored data.

INSTRUCTIONS for the LICENSE AGREEMENT:

IMPORTANT: This offer expires in 30 days. Please sign and return the attached document before this date. **If there is a reason why you will not be able to finalize your license within 30 days, please contact me at** llaplante@qualitymetric.com.

For the Student: Please follow the instructions below to execute the license agreement.

1. Sign the first page of the license agreement under "**LICENSEE**".
2. Please initial the remaining pages to acknowledge that you've read and agreed with license terms.
3. Return the entire agreement (**pages 1-5 and Appendix B**) to my direct fax at 401-642-9349 **OR** email a scanned copy to me at llaplante@qualitymetric.com.

Once the signed license agreement is received, we will release your survey forms and scoring materials.

Please let me know if you have any questions. I look forward to being working with you!

Kind Regards,

Lynda

Lynda LaPlante | Optum
OGSR Account Representative, Europe and Canada

Appendix 15: Postal questionnaire developed for cross-sectional study

Arthritis Research UK | primary care centre

Keele University

OWL

Opioids, Women and Libido

Study Unique Identifier: .....

INSTRUCTIONS FOR THIS QUESTIONNAIRE

Thank you for completing this questionnaire. The answers you give are **completely confidential**.

If you do not wish to complete the questionnaire **please return the questionnaire blank**. If you decide not to take part this will not affect your healthcare now or in the future.

Please read each question carefully.

Where there are boxes next to the responses please put a cross in the appropriate box or boxes:

e.g. Do you eat apples?

Yes ..... ☒ No ..... ☐

If a question needs an answer in numbers there will be boxes to write these in:

e.g. How many apples do you eat a day? | | 2 |

If a question has a lined section please answer write the answer in the space provided in BLOCK CAPITALS.

e.g. What is your favourite type of fruit?

APPLES

Where there is a scale from 0-10, please circle your answer:

e.g. How much do you enjoy eating fruit, on a scale of 0-10 where 0 is "not at all" and 10 is "as much as possible"?

Not at all ▼ As much as possible ▼

0 1 2 3 4 5 6 7 (8) 9 10

Please answer **ALL** the questions

When you have finished please check that you have answered all of the questions. Make sure you have read the information leaflet and completed the enclosed consent form if you agree to medical records review and then return the questionnaire in the enclosed envelope.

You do not need a stamp.

Section 1: Pain

This section asks about any pain you may have suffered in the past **6 months**.

1. How would you rate your pain on a 0 to 10 scale at the **present time**, that is right now, where 0 is "no pain" and 10 is "pain as bad as could be"?

2. In the past **six months**, how intense was your worst pain, rated on a 0 to 10 scale where 0 is "no pain" and 10 is "pain as bad as could be"?

3. In the past **six months**, on average, how intense was your pain rated on a 0-10 scale where 0 is "no pain" and 10 is "pain as bad as could be"? (That is, your usual pain at times you were experiencing pain.)

4. About how many days in the last **six months** have you been kept from your usual activities (work, school or housework) because of pain?

5. In the past **six months**, how much has pain interfered with your daily activities rated on a 0 to 10 scale where 0 is "no interference' and 10 is "unable to carry on any activities"?

6. In the past **six months**, how much has pain changed your ability to take part in recreational, social and family activities where 0 is "no change" and 10 is "extreme change"?

7. In the past **six months**, how much has pain changed your ability to work (including housework) where 0 is "no change" and 10 is "extreme change"?

Please go to next section

Section 2 – Medicines for pain

1. Tell us about any tablets, pills, patches or creams you may have used in the past **4 weeks** to reduce **pain**. Please include all treatments you have used. These may have been prescribed by your doctor, or you may have bought them without a prescription. If you have not used any pain relief in the last **4 weeks** leave this section blank.

   Here are some examples of common pain medicines: *paracetamol, ibuprofen, codeine, dihydrocodeine, nefopam, tramadol, buprenorphine, amitriptyline, pregbalin.* You may be taking one of these or you may be taking something completely different to help control your pain.

Medicine 1.

A. Name and Dose/Strength _____

B. How often do you use this medicine? ☐☐ per day **OR** ☐☐ per week

C. How much do you use per time? (e.g. 2 tablets) ☐☐ tablets/patches

D. How long have you been taking this medication? ☐☐ months

Medicine 2.

A. Name and Dose/Strength _____

B. How often do you use this medicine? ☐☐ per day **OR** ☐☐ per week

C. How much do you use per time? (e.g. 2 tablets) ☐☐ tablets/patches

D. How long have you been taking this medication? ☐☐ months

Medicine 3.

A. Name and Dose/Strength _____

B. How often do you use this medicine? ☐☐ per day **OR** ☐☐ per week

C. How much do you use per time? (e.g. 2 tablets) ☐☐ tablets/patches

D. How long have you been taking this medication? ☐☐ months

Medicine 4.

A. Name and Dose/Strength _____

B. How often do you use this medicine? ☐☐ per day **OR** ☐☐ per week

C. How much do you use per time? (e.g. 2 tablets) ☐☐ tablets/patches

D. How long have you been taking this medication? ☐☐ months

2. Tell us about any tablets, pills or creams you used in the past **6 months** to reduce pain but that you are **not currently using**. If there are no medicines that you have tried and now stopped then leave this question blank.

Medicine 5.

A. Name and Dose/Strength _____

B. Reason for stopping medicine please select one

It didn't help my pain	No longer needed as pain improved	I could not afford the medication	The medication made me feel unwell	I was worried about using the medication	I preferred to try something else
▼	▼	▼	▼	▼	▼
☐	☐	☐	☐	☐	☐

Medicine 6.

A. Name and Dose/Strength _____

B. Reason for stopping medicine please select one

It didn't help my pain	No longer needed as pain improved	I could not afford the medication	The medication made me feel unwell	I was worried about using the medication	I preferred to try something else
▼	▼	▼	▼	▼	▼
☐	☐	☐	☐	☐	☐

Medicine 7.

A. Name and Dose/Strength _____

B. Reason for stopping medicine please select one

It didn't help my pain	No longer needed as pain improved	I could not afford the medication	The medication made me feel unwell	I was worried about using the medication	I preferred to try something else
▼	▼	▼	▼	▼	▼
☐	☐	☐	☐	☐	☐

Medicine 8.

A. Name and Dose/Strength _____

B. Reason for stopping medicine please select one

It didn't help my pain	No longer needed as pain improved	I could not afford the medication	The medication made me feel unwell	I was worried about using the medication	I preferred to try something else
▼	▼	▼	▼	▼	▼
☐	☐	☐	☐	☐	☐

Section 3: Medical conditions and other medication

This section is about medicines you use for medical conditions that are **not pain conditions**. Tell us about any tablets, pills, injections or creams you may have used in the past **4 weeks**. Please include all treatments you have used. These may have been prescribed, or you may have bought them without a prescription, both are important.

Medicine

A. _____

B. _____

C. _____

D. _____

E. _____

F. _____

2. Which form of contraception do you currently use, if any? (cross all boxes that apply)

Progesterone only Pill	☐
Combined Oral Contraceptive Pill/Patch or Vaginal Ring	☐
Mirena Coil	☐
Copper Coil	☐
Implant (Nexplanon/Implanon)	☐
Condoms (Male or Female)	☐
Natural Family Planning	☐
Female Sterilisation	☐
Male Sterilisation (Vasectomy)	☐
Depot Injection (8-12 weekly injection)	☐
Diaphragm/Cap	☐
I do not use any form of contraception	☐

Please continue on the next page

3. Do you have or take treatment for any of the medical conditions below? (cross all boxes that apply)

- Anaemia ☐
- Anxiety ☐
- Chronic pain conditions ☐
- Depression ☐
- Diabetes ☐
- Epilepsy ☐
- High Blood Pressure ☐
- Hysterectomy ☐
- Menopause ☐
- Thyroid disease ☐
- Joint pain ☐
- Urinary Incontinence ☐
- Endometriosis ☐
- Chronic pelvic pain ☐
- None of the above ☐

4. Over the past 2 weeks, how often have you been bothered by any of the following problems?

		Most of the time	Some of the time	A little of the time	None of the time
a	Little interest or pleasure in doing things	☐	☐	☐	☐
b	Feeling down, depressed, or hopeless	☐	☐	☐	☐

Please go to next section

Section 4: Health and Wellbeing

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐	☐	☐	☐	☐

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
		▼	▼	▼
a	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
b	Climbing several flights of stairs	☐	☐	☐

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
		▼	▼	▼	▼	▼
a	Accomplished less than you would like	☐	☐	☐	☐	☐
b	Were limited in the kind of work or other activities	☐	☐	☐	☐	☐

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
		▼	▼	▼	▼	▼
a	Accomplished less than you would like	☐	☐	☐	☐	☐
b	Did work or other activities less carefully than usual	☐	☐	☐	☐	☐

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Have you felt calm and peaceful?	☐	☐	☐	☐	☐
b	Did you have a lot of energy?	☐	☐	☐	☐	☐
c	Have you felt downhearted and low?	☐	☐	☐	☐	☐

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

Please go to next section.

(IQOLA SF-12v2 Standard, English (United Kingdom) 8/02)

Section 5: Sexual Health

The following questions refer to your sex life during the past 6 months. Please answer every question with a YES or NO, depending on what applies to you most. Please be as frank as possible.

	Yes	No
1. Altogether, are you satisfied with your sex life?	☐	☐
2. Has the frequency of sexual contacts decreased compared to former times?	☐	☐
3. Do you have difficulties experiencing an orgasm during sex?	☐	☐
4. Do you sometimes have pain during sex?	☐	☐
5. Is your level of sexual desire satisfying to you?	☐	☐
6. As far as you know, is your partner satisfied with your sexual activity?	☐	☐
7. Altogether, are there any problems in your sex life?	☐	☐
8. Which of the following affects your sex life?		
a. Illnesses/operations of your own.	☐	☐
b. Illnesses/operations of your partner.	☐	☐
c. Problems in your relationship.	☐	☐
d. Other problems/stress.	☐	☐
9. Is your main problem regarding your sex life that you do not have a partner?	☐	☐
10. Do you consider masturbation a form of sex?	☐	☐
11. Would you like to change anything in your sex life?	☐	☐

If yes, what? _____

12. How often do you have sex?

☐☐☐ times/week ☐☐☐ times/month ☐☐☐ times/year

Please go to next section

Section 6: About you

1. How old were you on your last birthday? ☐☐ Years

2. What is your current marital status? (Please put a cross in one box only)

Married	☐	Widowed	☐
Separated	☐	Co-habiting (Living with a partner)	☐
Divorced	☐	Single	☐

3. Do you live alone?

Yes ☐ No ☐

4. Do you have any children?

Yes ☐ No ☐

If yes, how many? ☐☐

5. What is your weight? ☐☐ stones ☐☐ pounds **OR** ☐☐☐ kgs

6. What is your height? ☐☐ feet ☐☐ inches **OR** ☐☐☐ cms

7. Do you smoke cigarettes?

Never smoked	☐
Ex-smoker	☐
Current Smoker 10 cigarettes or less per day	☐
Current Smoker 11-20 cigarettes per day	☐
Current Smoker 21+ cigarettes per day	☐

8. On average how often do you drink alcohol? (Please put a cross in one box only)

Daily or most days	Once or Twice a week	Once or Twice a month	Once or twice a year	Never
☐	☐	☐	☐	☐

9. Do you use any illegal drugs?

Yes ..... ☐ No ..... ☐

If yes, what? _____

10. Which of the following best describes your current employment status? (select one)

Working in a paid job ..... ☐
Working in a voluntary job ..... ☐
Employed but currently off sick ..... ☐
Looking after the home/children ..... ☐
Retired ..... ☐
Student ..... ☐
Other ..... ☐

If other, what is your current situation? _____

11. What is your ethnic group? Choose ONE option that best describes your ethnic group

White ..... ☐
Asian ..... ☐
Black ..... ☐
Mixed ..... ☐
Other ..... ☐

If other, please describe _____

Please go to next section

Section 7: Consent Form

Thank you for taking the time to complete this questionnaire.

The questionnaire is not meant to be distressing in any way. However, if the questionnaire leads to distress, unpleasant memories or thoughts, we would encourage you to contact your General Practitioner. You may also wish to contact an independent mental health support group, which does not require referral from a doctor or a nurse. All calls are free (call back also available), confidential and support is provided by trained staff. The phone numbers of these support groups are listed below.

MIND 0300 123 3393

Samaritans 116 123

For further information on sexual health visit the following website:

www.fpa.org.uk/your-body/sexual-problems

Please ensure that you have read the enclosed information sheet that explains about the study.

Please read, complete and sign the consent form on the following page.

Appendix 16: Cross-sectional study patient information leaflet

Study Information Sheet

OWL

Keele University

Invitation

We would like to invite you to take part in a research study about painkillers called opioids such as codeine and morphine and reproductive and sexual health in women with joint pain.

The study is entitled OWL (Opioids, Women and Libido).The study is being undertaken by a team at the Research Institute for Primary Care and Health Sciences, Keele University.

Why have I been invited?

You have been invited because you are registered at a General Practice that is part of the West Midlands Clinical Research Network. Within the last 6 months you have seen your GP about joint pain and have also been prescribed an opioid pain killer. **If you are not currently using opioid pain killers we would still like you to take part in the study.**

What is the purpose of the research?

Opioid painkillers are being prescribed more commonly for long-term pain, for example joint pain. The evidence for their use is mainly based on use in cancer pain. We do not know very much about the sexual health of women who take opioid painkillers for joint pain, which is why we are doing this study. One of the things we are interested in is how libido is related to opioids.

What do I need to do if I choose to take part?

The study involves a single **questionnaire**. The questionnaire should take you approximately **20 minutes** to complete. There is also a consent form asking if we may access anonymised information from your medical records. If you do not wish to consent to access to your medical records please still consider completing the questionnaire, as your answers are still important to us. Once completed, please post both the questionnaire and the consent form back to us in the enclosed stamped addressed envelope.

If you consent to being contacted for future research we will store your name and address in a password protected database for up to 5 years after the completion of the study. If you consent to contact this does not mean you have to take part in future studies and you can ask to be removed from the list at any time by contacting us via the methods below.

Do I have to take part?

No, your involvement is **voluntary** and you do not have to take part if you do not want to. You may either complete the questionnaire with or without consent for medical record review or choose to not complete the questionnaire. Choosing to not take part will not affect your usual medical care in anyway. If you do not wish to take part please return the

questionnaire blank. If you do not want to take part but do not return the blank questionnaire, you will be sent two reminders about the study following this invitation.

What are the benefits/risks of taking part?

Taking part will help improve knowledge around use of opioid painkillers for future patients. There will be no direct benefit to you. We do not foresee any risks from taking part.

Who is funding the project?

The study is funded by Professor Christian Mallen's National Institute for Health Research Professorship.

Who will have access to information about me?

Your participation will be kept completely confidential. The paper questionnaires (including your signed consent form) will be returned to Keele University, where they will be stored in separate locked cabinets with limited access. Other than your consent form, your information and data will be anonymised (your name removed) and you will be assigned a unique study code so we can link your answers to the information from your medical records (if you have agreed to give us access). Digital information will be stored on a secure password protected university network computer.

What will happen to the results of the study?

The results will be written up for a PhD thesis and publication in a scientific journal.

Has the research study been ethically approved?

NHS ethical approval has been granted (IRAS 210681). Approval has also been granted from the Health Research Authority to conduct this research.

What if there is a problem?

If you have concern about any aspect of the study and wish to speak to the researcher then please contact Dr Emily Wersocki by email at e.wersocki@keele.ac.uk or by telephone on 01782 734889. Alternatively if you do not wish to contact the researcher please write to Dr Clark Crawford Head of Research Integrity, Directorate of Engagement and Partnership, IC2 Building, Keele University, ST5 5NH, or email research.governance@keele.ac.uk , or telephone 01782 733371. If this invitation or questionnaire has caused you any distress please visit www.fpa.org.uk/your-body/sexual-problems for further information and support.

Further information and contact details

If you would like further information please contact the OWL study coordinator, Emily Wersocki by email at e.wersocki@keele.ac.uk or via phone 01782 734889.

Appendix 17: Cross-sectional study consent form

OWL

IRAS 210681

Consent Form

Keele University

Participant Unique Identifier:……..

Please read the patient information leaflet and then complete the following consent form, and sign below.

Consent form

Please answer each statement by putting your INITIALS in one box on each line

	YES	**NO**
I give my permission for my medical records to be reviewed……	☐	☐
I am happy to be contacted again (this does not mean that you must take part in future - you are just agreeing to be contacted again)…….	☐	☐

Signed……Date……

Only if you have answered yes to being contacted for future studies, please print your name and address below**,**

……

……

……

……

Even if you would prefer us not to review your medical records or contact you in the future about linked studies, the answers you have given in this questionnaire will still be very important to us.

Please return your questionnaire in the FREEPOST (no stamp needed) envelope provided

Thank you for your help with this research project