

An exploration of strong opioid utilisation in non-cancer pain patients in UK primary care, 2000-2010

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Dedications

In the name of God, the most merciful, the most compassionate. This thesis is dedicated for the sake of God.

This thesis is also dedicated to my beloved parents Sureer Mohammed and Adan Hag Hersi.

Words cannot express my gratitude and appreciation for everything you do.

Abstract

Background

Opioids are the most potent analgesics available and their treatment is well established in cancer and acute pain. However, their long-term use in non-cancer pain is worrisome due to insufficient evidence on long-term effectiveness and safety. Population-based research examining the utilisation of opioids in non-cancer pain patients in UK primary care remains limited and little information exists on patients receiving long-term therapy.

Aims

This thesis aimed to examine the demographics, clinical traits, prescribing patterns and healthcare use of non-cancer pain patients prescribed strong opioids in primary care, with a focus on long-term strong opioid use.

Methods

The thesis was a retrospective observational study using the Clinical Practice Research Datalink. Prescription data of four strong opioids (morphine, buprenorphine, fentanyl and oxycodone) issued between 2000-2010 to adults (aged ≥18 years) without cancer diagnosis 12 months within the date of first prescription use were included. The annual prevalence and incidence of non-cancer pain patients prescribed strong opioids over the 11 years were initially assessed using joinpoint regression analysis, and the users' demographic and clinical characteristics were explored descriptively. The numbers of prescriptions per patients, total number of days of drug supply, and total oral morphine equivalent daily dose (OMED) were subsequently calculated annually and compared between long-term (>90 days/year) and short-term (≤90 days/year) users. Multivariate linear regression modelling with generalized estimating equations was consecutively used to identify baseline and time-varying covariates linked to long-term strong opioid use. Lastly, long-term strong opioid users' primary and

secondary healthcare use was quantified using CPRDs' data link with Hospital Episode Statistics (HES), and the nature of hospital admissions and patient-level factors of influence were determined by multivariate regression data analysis.

Results

A total of 135,941 non-cancer pain patients (63.34% female, mean age 66.34±17.98 years) were prescribed strong opioids and were included in the analysis. The incidence of long-term prescribing (>90 days) continued to increase by 16.96% per year (95%CI: 13.70%, 20.30%, p<0.001) from 3.60 (95%CI: 3.38, 3.82) per 10,000 person-years in 2001 to 12.75 (95%CI: 12.41, 13.10) per 10,000 person-years in 2010. The mean number of pain diagnoses amongst long-term users was 3.00±2.16, with back pain, abdominal pain and osteoarthritis presenting the most common diagnostic disorders, and the mean number of co-morbidities was 2.04±1.70. Depression and anxiety were prevalent in 50.02% and 22.13% of long-term users, respectively.

The mean daily oral morphine equivalent dose (OMED) of long-term users (95.88±109.03 mg/day/year) was almost twice that of short-term users (54.80±54.55mg/day/year). Over a quarter (26.01%) of long-term users received high oral morphine equivalent daily dose and their mean annual OMED was 221.19±148.07mg/day and mean annual days' supply was 277.05±84.55 days.

Forty-one percent of long-term users had one or more all cause in-patient admissions during the study period, and a rising trend of admission spells was noted annually by 28.16% (95% CI: 26.40, 29.90, p<0.001). Musculoskeletal pain disorders were the main cause of hospital admissions and re-admissions. Factors associated with hospitalisation included; greater GP visits per year (>3 consultations/year), >120mg morphine equivalent daily dose (aRR: 1.37; 95%CI: 1.27, 1.49) and co-prescriptions of psychoactive medications, including

antidepressants (aRR: 1.07; 95%CI: 1.00, 1.14), benzodiazepines (aRR: 1.17; 95%CI: 1.09, 1.26) and non-benzodiazepines (aRR: 1.15; 95%CI: 1.05, 1.27).

Conclusions

Prescribing of strong opioids over the 11 years was characterized by a shift towards long-term prescribing. Primary care non-cancer pain patients exposed to strong opioids long-term were typified by multiple pain and co-morbid illnesses that included common psychiatric disorders, which suggest complex, and vulnerable, high-risk patients that are susceptible to negative health consequences. The thesis has identified several covariates linked to strong opioid-utilisation and healthcare use, which exemplifies key findings that can be used to inform clinical decision-making, targeted management interventions and monitoring of non-cancer pain patients treated with strong opioids long-term.

Conference presentations

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Awards

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List of abbreviations

aOR	Adjusted odds ratio
aRR	Adjusted risk ratio
APC	Annual percent change
BNF	British National Formulary
BMI	Body Mass Index
BPS	British Pain Society
CPRD	Clinical Practice Research Datalink
CNCP	Chronic non-cancer pain
CBT	Cognitive behavioural therapy
CRD	Current registration date
COPD	Chronic obstructive pulmonary disease
CNS	Central nervous system
COXs	Cyclo-oxygenase inhibitors
DH	Department of Health
GP	General Practice/Practitioners
GMS	General Medical Services
GEE	Generalized estimating equation
HES	Hospital Episode Statistics
ISAC	Independent Scientific Advisory Committee
INPS	In Practice Systems Ltd
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
IR	Immediate release
LA	Long-acting
MHRA	Medicines and Healthcare product Regulatory Agency
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
MI	Multiple imputation
MSK	Musculoskeletal
MeSH	Medical Subject Headings
NIHR	National Institute for Health Research

List of abbreviations

NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NDD	Numeric daily dose
NSAID	Nonsteroidal anti-inflammatory drug
NRS	Numerical rating scale
OXMIS	Oxford Medical Information Systems
OMED	Oral morphine equivalent dose
QOF	Quality and Outcomes Framework
QOL	Quality of life
RCT	Randomized controlled trial
SA	Short-acting
SR	Slow-release
SHA	Strategic health authority
UTS	Up-to-standard
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WHOCC	WHO collaborating Centre for Drug Statistics Methodology
95%CI	95% Confidence Interval

Chapter 1 Introduction

In the UK, chronic non-cancer pain is increasingly recognised as a common health problem. Almost half of the adult population report chronic pain at any point, and recent data suggest that an estimated 28 million adults are impacted by chronic pain that lasts for more than three months. Chronic non-cancer pain is pervasive, debilitating and interferes significantly with daily life and activities as a function of patients' pain severity.

Treatment options for chronic non-cancer pain are available and include pharmacological interventions such as analgesics and non-pharmacological such as physiotherapy and cognitive behavioural therapy. However, current interventions provide limited capacity in preventing and relieving long-term pain and their impact is frequently short-lived. As such, opioids could be seen as a viable alternative and a plausible treatment option.

However, while the use of opioids is justified by robust evidence in acute pain, in end of life pain and in short-term aggravation of chronic pain, their long-term use in chronic non-cancer pain is still a matter of debate.

What is more is that the experience of opioids in cancer pain has provided distinct observations which has confounded known pharmacological traits of the drug class. For example, cancer patients prescribed opioids rarely experience euphoria, and neither tolerance nor dependence are substantial clinical issues. Furthermore, analgesic inefficiency and treatment withdrawals due to intolerable side-effects with the use of opioids are rarely reported in cancer patients.

Such observations, and the principle that the relief of pain is a fundamental human right and that uncontrolled pain would lead to long-term deleterious physical effects, reduced

independence, dignity and decision-making abilities, have been some of the initial arguments used in support of chronic opioid therapy in non-cancer pain. The latter arguments have been based on the analgesic the superiority of opioids' potency compared to non-opioid interventions.

Conversely, chronic non-cancer pain is markedly and fundamentally different from either acute or cancer pain. Chronic non-cancer pain can have an unclear aetiology and can be affected by psychosocial factors, which makes long-term management a challenge. Moreover, there is a need for sustained treatment of pain while ensuring a level of functioning, improvement in lifestyle and quality of life (QoL) over long periods. Whilst there is evidence of some degree of pain reduction amongst chronic non-cancer pain patients using opioids over short-term periods, there is no high-quality evidence in the literature confirming sustained pain relief, improved function and QoL over long-term periods with opioid therapy.

Equally, empirical studies have found that opioid use long-term is beset by negative physical and psychological effects, which include impairment of immune and endocrine functions, fractures and falls, disorders of nocturnal respiratory control, worsening of pain (opioid-induced hyperalgesia), aberrant drug-related behaviours, overdose, and death. This is often cited as a cause for considerable concern, and further questions the role of the potent drugs for such pain.

Prescribing of opioids long-term is undoubtedly a complex endeavour, and the optimization of their role in pain management needs to be balanced against risks of harm. Present UK guidance is standard in that it acknowledges the potential harms of opioid prescription use and the significant clinical uncertainties that exist around the effectiveness of continuous opioid use.

However, persistent long-term pain amongst the adult population invariably leads to patients seeking healthcare advice and management in primary care. Yet, gaps exist in the knowledge of opioid utilisation in patients with chronic non-cancer pain in UK primary care. In particular, and importantly, treatment patterns in clinical settings involving stronger opioids, which may carry a greater propensity of health risks, is an area of research that has not been well characterized.

The majority of opioid utilisation studies in primary care have focused on short to medium term uses, usage in specific non-cancer pain conditions, study samples from small geographic areas and the use of survey/cross-sectional study designs as opposed to longitudinal follow-up investigations. Information on who is likely to receive opioids/stronger opioids for non-cancer pain over prolonged periods, factors affecting the utilisation, and patterns of healthcare use is a gap in the current literature. Given the ambiguous and challenging context of opioid utilisation in chronic non-cancer pain, a national examination of the utilisation with respect to stronger opioids would be an important initial step in elucidating distinct facets of the utilisation and the patients treated that may need to be addressed.

Thesis outline

The thesis consists of seven chapters. The content of each chapter is outlined below (Figure 1-1).

Chapter 2 provides an overview of the literature to describe the evidence-based knowledge of long-term opioid use in non-cancer pain. Research on the utilisation of opioids in non-cancer pain in UK primary care is then investigated; what is currently known is described and progress in the field is traced. This is followed by an outline of the aims and research questions of the

thesis. The chapter also provides an overview and a justification for the use of the Clinical Practice Research Database (CPRD) as the source of data collection and analysis in the thesis.

Chapter 3 aims to provide a comprehensive account of prescription trends of strong opioids between 2000-2010, within a sample of non-cancer pain patients registered in general practices that have contributed data to CPRD. The chapter also presents overall trends in the incidence and prevalence of strong opioid prescription users and users of the drugs long-term, and provides a quantitative overview of the changes in the measures over time.

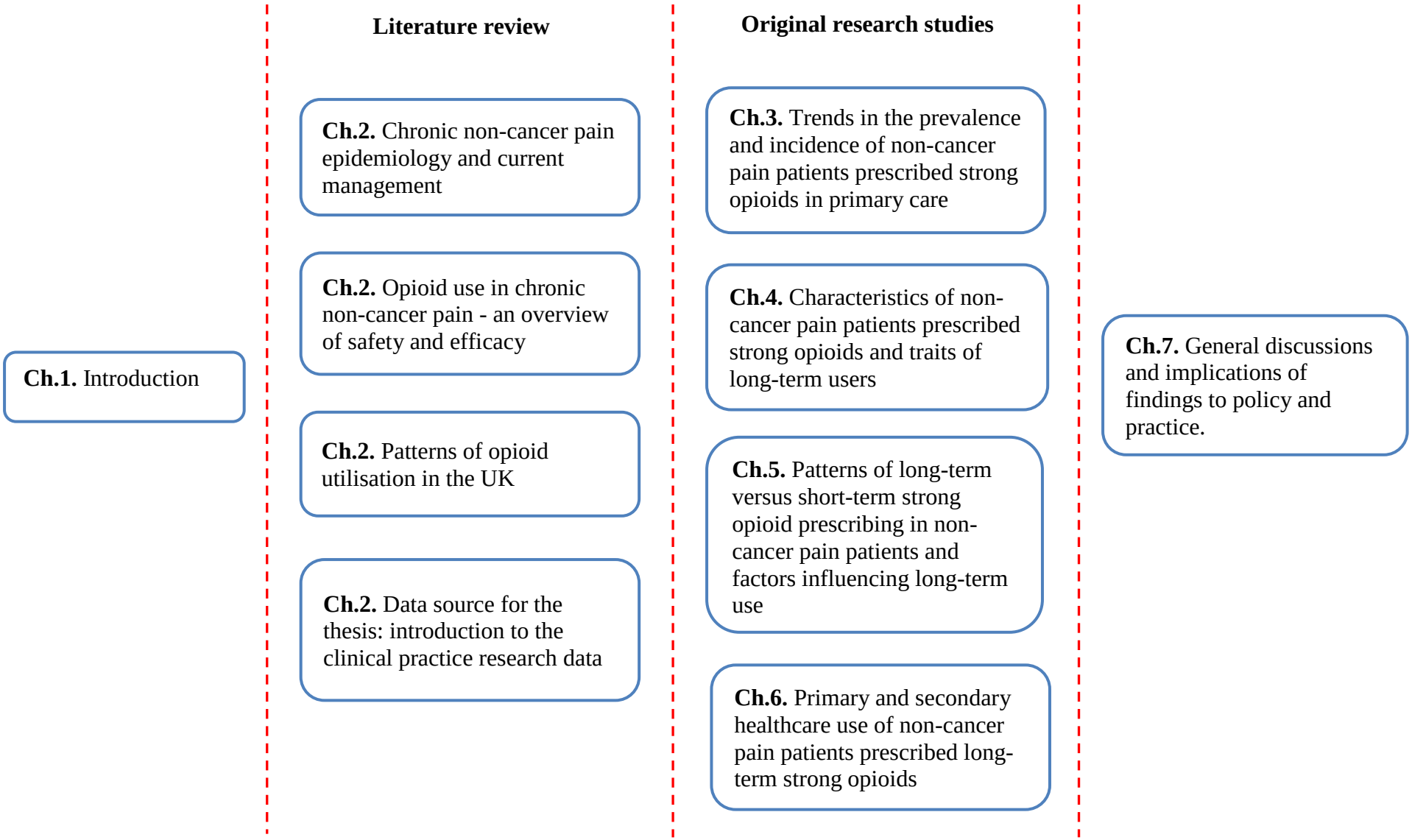
Chapter 4 profiles the sample study of non-cancer pain patients prescribed strong opioids identified in chapter 3. Their socio-demographic characteristics and co-existing morbidities are explored and a description of the traits of patients prescribed strong opioids long-term is explored.

Chapter 5 investigates the longitudinal prescribing patterns of long-term strong opioid users versus short-term users. Utilisation measures, such as the number of prescriptions issued per user, number of prescription days supplied and the oral morphine equivalent daily dose are calculated and presented according to the user type. Factors linked to long-term strong opioid use are also determined using multivariate regression analysis.

Chapter 6 focuses on long-term strong opioid users and presents a quantification of their primary healthcare use. In addition, referral to pain specialists and patterns of users' hospital admission over the 11-years is also examined. Factors influencing hospitalisation of long-term strong opioid users are analysed through the use of multivariate regression modelling.

Chapter 7 highlights the main findings of the thesis and provides a discussion of the implications of the findings for policy and practice. In addition, directions for future research based on the findings are suggested.

Figure 1-1 A flow diagram of the structure of the thesis



Chapter 2 Overview of the literature

2.1 Chronic non-cancer pain

2.1.1 Definition

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, or both"* [(1)].

The definition takes into consideration that although tissue damage or a potential pathophysiological cause could be the tracing point to a pain stimuli, this is not always the case, since pain and its strong emotional response is also reported in the absence of tissue damage. In addition The IASP specifies that *"pain is always subjective, and each individual learns the application of the word through experiences related to injury in early life"*, thus highlighting individual differences in the subjectivity of pain [(1)].

Pain is frequently categorised on the basis of the duration of the pain, and primarily as either acute or chronic [(2)]. Acute pain happens swiftly and as a response to an immediate injury or damage, such as a sprain, cut, burn or fracture. This type of pain acts as an essential biological warning signal and serves to protect the injured area. It is usually short-lived, and in most cases the cause is entirely known and can be managed. Furthermore, as the healing process occurs, the pain intensity eventually subsides [(3)].

Conversely, pain that perseveres and outlasts its usefulness as a warning system is termed chronic pain. This type of pain becomes a debilitating disease in its own right. The IASP defines chronic pain varyingly as "*pain without apparent biological value*" or as "*pain that persists beyond the normal tissue healing time*" or as "*a persistent pain that is not amenable as a rule*

to treatment based upon specific remedies". The definitions encompass a large number of chronic pain conditions with distinct differences in characteristics; for example some conditions, such as rheumatoid arthritis, are less likely to be reversible in their healing, whereas migraine headaches remit (i.e. heal) and recur [1]. Notwithstanding differences between chronic pain conditions, many research studies use three months as an indicator of chronic pain [4-9].

Chronic pain that is not embedded in or originates from cancer is described as chronic non-cancer pain (CNCP). Compared to acute pain, chronic non-cancer pain is more insidious due to its prolonged interference with patients' physical, psychological state and quality of life, but also due to, in many instances, the difficulty in its diagnosis by healthcare professionals [3].

2.1.2 Prevalence

The prevalence of various CNCP conditions in the UK has been highlighted in a number of studies (Table 2-1). However there has been wide variability in the reported national population estimates [4-25]. The first study to directly report the prevalence of chronic pain was conducted amongst 1,037 households of the general population, and was published in 1991 [20]. The author telephone-surveyed British household participants, and reported an 11.5% prevalence of chronic pain that lasted more than 3 months.

In 2001, a study conducted in the Grampian region of South East Scotland found that 50.4% of 3,605 primary care patients reported chronic pain (> 3 months) [12]. The author standardized the study sample to the age and gender of the general population and concluded an equivalent estimated prevalence of chronic pain (defined as >3 months) of 46.5% in the adult population.

In 2006, a large European survey of the prevalence of chronic pain was published [19]. This included 15 European countries, and reported a point prevalence of 13% in the UK with the median duration of pain being 5.9 years. A more recent study by Fayaz A et al. (2016) systematically reviewed published studies from the 1990s onwards and concluded a pooled prevalence estimate of chronic pain in the general population to be as high as 43.5% (95% CI: 38.4% to 48.6%) [26]. The study concluded a corresponding estimate of 28 million individuals in the UK would be affected by chronic pain at some point in their life-time. This is considerably higher than the prevalence rate estimated by the large European telephone survey mentioned earlier, which reported 7.8 million chronic pain sufferers in the UK.

A number of studies have focused on estimating the prevalence of specific chronic pain conditions, particularly that of chronic widespread pain, osteoarthritis and chronic low back pain in primary care (Table 2-1). The prevalence of chronic widespread pain (> 3 months) was reported by Croft P et al. (1993) to be 11.2% in a primary care sample of 2,034 across the North of England [21]. Similarly, Macfarlane GJ et al. (1999) conducted a population-based survey in Greater Manchester and found that the prevalence of chronic widespread pain was 13% [16]. Aggarwal VR et al. (2006), on the other hand, focused on surveying adults in primary care practices in the North West of England, and yielded a prevalence of chronic widespread pain of 15.0% [14].

Similarly, the precise prevalence estimate of osteoarthritis is elusive in studies, and is mainly due to problems associated with definition, diagnosis, and the use of different general practice databases. For example, Jordan K et al. (2007) compared consultation rates (the proportion of the population with a diagnosed consultation over a defined period of time) of musculoskeletal conditions, which included osteoarthritis, using three national general practice databases and

one national database, and found that the percentage of recorded consultations that were for osteoarthritis ranged from 9.4% (GPRD, 2001), 9.8% (CiPCA, 2001), 11.9% (RCGP WRS, 2001) to 19.2% (MSGP 1991/1992) [27].

Differences in the estimation of the prevalence of chronic non-cancer pain between studies could also be explained by the differences in the time period in which the studies were conducted, the study designs, sample size, sampled regions, and differences in the response rates between studies (Table 2-1) [5-25]. Despite this, common consistent demographic patterns such as the age of participants reporting chronic pain and the significant interference of chronic pain with patients' general health and well-being were observed across a number of the studies [9, 12, 15].

For instance, a postal questionnaire study in the South East of England found that the overall crude prevalence of musculoskeletal-related chronic pain was 38% [9]. This increased with age, and the prevalence was greatest in those aged ≥75years (46%). Sufferers in the study were more likely to report lower quality of life, psychological distress and pain-related disability. Similarly a regional study in the Grampian area of Scotland identified that 6.3% of patients had severe debilitating chronic pain, which was significantly linked to age, with an estimated prevalence of 3.4% in 25–34 years olds in contrast to 10.6% in ≥ 75 years olds [12].

In a different postal questionnaire study conducted in North Staffordshire, 66.9% reported to have experienced pain that had lasted more than 3 months [15]. Approximately 14.3% of the responders reported chronic pain, of which chronic back pain was the most common complaint (76.5%). In addition, one in four had pain-related disabilities, poorer self-rated health, anxiety and depression.

2.1.2.1 Trends in prevalence

While the studies mentioned so far have examined the prevalence of CNCP at a snapshot in time, several studies have considered trends in the prevalence of CNCP over consecutive time-intervals to assess the magnitude of change of CNCP in the general population. Such information is currently only available for certain CNCP conditions.

Harkness EF et al. (2005) conducted two population-based surveys 40 years apart, one in the 1950s, and later in 1990s, in the North West region of England [28]. The study examined changes in the prevalence of three musculoskeletal-related pain conditions, which included low back pain, shoulder pain and widespread pain. The result demonstrated a 2 to 4-fold increase in the prevalence of each condition over the study period. For low back pain, the prevalence had increased two-fold (PRR: 2.0, 95%CI: 1.4–2.8), for shoulder pain the rise was almost four-fold (PRR: 3.9, 95%CI: 2.7–5.7), and for widespread pain, the increase was just over three and half-fold (PRR: 3.6, 95%CI: 2.2–5.8). The study also identified significant increases in the prevalence of all three conditions amongst women rather than men. The author suggested that the changes in prevalence could possibly be explained by factors such as enhanced awareness of pain, willingness to report pain, and a rise in mental disorders which are known to be associated with pain [28].

Following Harkness EF et al.'s (2005) investigation, Waxman and colleagues (2000) conducted a postal questionnaire study in Bradford to compare the prevalence of low back pain in 1994 and 1997 [29]. The average annual prevalence was found to be 44%, whereas the average lifetime prevalence of the condition was 59%. The study estimated a yearly incidence rate of 4%, and there was evidence of increased patterns of back pain-related disability in patients who reported persistent low back pain. In 1994, 26% of patients with consistent low back pain

reported to also have difficulty with activities of daily living (ADL), and this had increased to 75% by 1997.

Meanwhile, Yu D et al. (2015) examined the total yearly consultation incidence of osteoarthritis between 2003 and 2010 using the Consultations in Primary Care Archive (CiPA) database [30]. The database holds anonymised medical records from 11 general practices throughout North Staffordshire. Although as expected, the incidence of osteoarthritis rose in parallel with age, increasing to 3% in the age-group 75-84 years, the data also revealed an unusual increase in the incidence of osteoarthritis in the patient group between 35-44 years from 0.3/1000 persons (95%CI: 0.1, 0.8) in 2003 to 2.0/1000 persons (95%CI: 1.3, 2.9) in 2010. This is particularly noteworthy not only because a younger age is not a usual risk factor for osteoarthritis but also because such trend presents a public health concern. The author speculatively relates the findings to be plausibly associated with the rise in the prevalence of obesity (which encompasses the periods of the study), which would considerably elevate the risk of osteoarthritis [31, 32].

Table 2-1 Studies reporting the prevalence of chronic pain in the UK

Study	Study design	N	Source of sample/method of data collection	Type of chronic pain	Prevalence of chronic pain estimated
Croft P et al., 2003 [5]	Case-control	11,797	Data obtained from: GP practice participants/Postal questionnaire	Regional & widespread pain	14.3% had widespread pain and 12.3% chronic widespread pain
Gale CR et al., 2012 [8]	Cohort	11,971	Data obtained from: UK Data Archive, University of Essex/ Questionnaire	Chronic widespread pain	14.4% reported chronic pain (>3months)
Smith BH et al., 2004 [6]	Cross-sectional	11.797	Data obtained from: RCGP study (1968)/ Postal questionnaire	Any chronic pain	38.4% reported chronic pain (>3 months)
Jones GT et al., 2007 [7]	Cohort	10,453	Data obtained from: 1958 British Birth Cohort Study/Postal questionnaire	Chronic widespread pain	12.2% reported chronic widespread pain (>3 months)
Torrance N et al., 2013 [10]	Cross-sectional	10,000	Data obtained from: GP practices from 5 UK locations/Postal questionnaire	Any chronic pain and neuropathic pain	48.5% reported chronic pain (> 3months), 8.9% reported any chronic pain with neuropathic pain
Bridges S et al., 2011 [33]	Cross-sectional	8,599	Data obtained from: 2011 Health Survey for England/Questionnaire	Any chronic pain	31% of men and 37% women reported chronic pain (>3 months)
Vandenkerkhof EG et al., 2011 [11]	Case-control	8,572	Data obtained from: 1958 British Birth Cohort Study/Questionnaire	Regional & widespread pain	41% reported regional pain and 12% widespread pain (>3 months)

(Continued) Table 2-1 Studies reporting the prevalence of chronic pain in the UK

Study	Study design	N	Source of sample/Method of data collection	Type of chronic pain	Prevalence of chronic pain estimated
Torrance N et al., 2006 [4]	Cross-sectional	6,000	Data obtained from: GP practices in Leeds, Grampian area, London/ Postal questionnaire	Chronic pain and Chronic pain of neuropathic origin	48% reported chronic pain (>3 months) and 8.2% chronic pain of neuropathic origin
Smith BH et al., 2001 [12]	Cross-sectional	4,611	Data obtained from: GP practices in Grampian region/ Postal questionnaire	Any chronic pain	50.4% reported any chronic pain (>3 months), 14.1% reported significant chronic pain
Jones GT et al., 2015 [13]	Cross-sectional	4,600	Data obtained from: GP practices in Grampian region/ Postal questionnaire and clinical examination	Fibromyalgia	31% reported fibromyalgia
Aggarwal VR et al., 2006 [14]	Cross-sectional	4,200	Data obtained from: GP practices in North West England/Postal questionnaire	Chronic widespread pain and chronic orofacial pain	15% reported chronic widespread pain and 7% orofacial pain (>3 months)
Parsons S et al., 2007 [9]	Cross-sectional	4,171	Data obtained from: GP practices in South East England/Postal questionnaire	Musculoskeletal related chronic pain	Crude chronic pain (> 3 months) reported by 38% participants.
Mallen C et al., 2005 [15]	Cross-sectional	2,389	Data obtain from: GP practices in North Staffordshire/ Postal questionnaire	Chronic pain	14.3% reported chronic pain (>3 months)

(Continued) Table 2-1 Studies reporting the prevalence of chronic pain in the UK

Study	Study design	N	Source of sample/Method of data collection	Type of chronic pain	Prevalence of chronic pain estimated
MacFarlane TV et al., 2010 [17]	Cross-sectional	3,950	Data obtained from: GP practices in North West England/ Postal questionnaire	Chronic widespread pain	15.3% reported chronic widespread pain (>3 months)
MacFarlane GJ et al., 1999 [16]	Cross-sectional	3,004	Data obtained from: GP practices in Manchester/ Postal questionnaire	Chronic widespread pain	13% reported chronic widespread pain (>3 months)
Elliott AM et al., 1999 [22]	Cross-sectional	5,036	Data obtained from: GP practices in Grampian region/Postal questionnaire	Any chronic pain	50.4% reported chronic pain (>3 months)
Thomas E et al., 2004 [18]	Cross-sectional	11,055	Data obtained from: GP practices in North Staffordshire/ Postal questionnaire	Any chronic pain	72.4% reported any pain <4 weeks and 12.5% reported wide spread pain
Breivik H et al., 2006 [19]	Cross-sectional	46,394	Data obtained from: 15 European countries and Israel/Telephone survey	Any chronic pain	UK; 13% reported chronic pain (>6 months)
Croft P et al., 1993 [21]	Cross-sectional	2,034	Data obtained from: GP practices in North England/ Postal questionnaire	Chronic widespread pain	11.2% reported chronic widespread pain (>3 months)

(Continued) Table 2-1 Studies reporting the prevalence of chronic pain in the UK

Study	**Study design**	**N**	**Source of sample/Method of data collection**	**Type of chronic pain**	**Prevalence of chronic pain estimated**
Bowsher D et al., 1991 [20]	Cross-sectional	1,037	Data obtained from; GP practices/Telephone survey	Any chronic pain	11.5% reported chronic pain (>3months)
Palmer KT et al., 2005 [24]	Cross-sectional	2,632	Data obtained from: GP practices in North Somerset, England/ Mailed questionnaire	Chronic low back pain	11% reported chronic low back pain (>6months)
Hillman M et al., 1996 [23]	Cross-sectional	3,184	Data obtained from: GP practices in Bradford, England/ Postal questionnaire	Chronic low back pain	26% reported chronic low back pain (>3months)
McAlindon TE et al., 1992 [25]	Cross-sectional	513	Data obtained from a GP practice in Bristol/ Postal questionnaire	Radiographic knee osteoarthritis	13% (>55 yrs) had radiographic evidence of osteoarthritis

2.1.3 Economic impact

Chronic pain does not only have a direct impact on individual patient's well-being and quality of life but it also poses a significant financial burden due to its effect on the labour market and healthcare resource use [34]. The economic cost of CNCP has been proven more so for musculoskeletal pain conditions, such as low back pain and osteoarthritis, than any other pain disorders [35].

Low back pain is a commonly occurring health condition with an estimated 1-year incidence rate of 36% [36]. The condition has a larger indirect economic impact than many other conditions due to its significant leverage in rates of absenteeism, decreased levels of work productivity and the risk of departure from employment. For example, a cost of illness study in 1998 approximated that £9,090 million were lost due to back pain-related inability to work, with average days of incapacity to work lasting up to 232 days [35]. Similarly, in 2014 the Office for National Statistics estimated that there were 30.6 million days lost in the labour market due to sickness attributed to back pain, and it is reported that in any given year, the condition is the main reason for long-term sick leave [37]. Meanwhile, Watson PJ et al. (1998) reported that during 1994, £1.29 million was paid in Disability Living Allowance to medically certified back pain sufferers, and the study noted that this corresponded to an excess cost of £3.16 million per 100,000 of the working population [38].

Likewise, the loss of economic productivity due to osteoarthritis is as significant as back pain, with a total cost to the UK economy estimated at 1% of the annual gross national product [39]. According to the Department of Work and Pensions, 36 million working days were lost between 1999-2000 due to osteoarthritis, which caused a loss of productivity of £3.2 billion

[40]. At the same time, £43 million and £215 million were spent on community and social services respectively to manage osteoarthritis-related complications [40].

Apart from the indirect financial cost, the direct cost, which typically consists of direct medical costs arising from treatment in primary, secondary or tertiary health care settings, and in some cases direct non-medical costs related to social care within the community, has also been determined for the conditions [35, 41, 42]. The direct cost of back pain to the National Health Service (NHS) has been estimated to be £1 billion per year [35]. Of this; 37% of the cost was spent on physiotherapy, 31% on the use of hospital services, 14% was related to service use provided in primary care, 7% was for medication, 6% was for community care and 5% was for radiology and imaging assessments.

Meanwhile, a large proportion of the direct cost of osteoarthritis treatment is due to the cost of surgery. In 2010, this was found to account for 85% of the total direct treatment cost of £1 billion, and within the same year 76,759 primary total hip replacement procedures were conducted, which was a 6% surge from 2009 and resulted in a total cost of £426 million [41, 42].

It is evident that CNCP patients will initially seek care in primary care, which is the first port of call in the healthcare system for most patients [43]. Management of chronic pain patients in primary care constitutes up to 4.6 million appointments per annum, at a cost of £69 million, which includes costs related to diagnostic procedures, treatment and referrals [43]. Moreover, between 1997 and 1998, the estimated total cost of GP consultations related to back pain mounted to £140.6 million, of which £108.2 million were associated with care at surgeries and £32.4 million were costs due to care provided in patients' homes [35]. This suggests that back pain is associated with significant expenditure; however, the degree of disability and expenses

of other types of non-cancer pain conditions in the general population is not available for comparison.

More recent data have been able to estimate cost related to analgesic medication usage in primary care in England. The prescribing of topical NSAIDs between 2005 and 2006 was £8.5 million, and that of oral NSAIDs was £25 million. By 2010, and accounting for inflation, the cost of both topical and oral NSAIDs had increased to £19.2million and £25.65, respectively [44]. Further to this, since 2004, spending on opioids has increased by 10% (by £6.1 million), with a greater increase in the cost observed for dispensing prescriptions for buprenorphine (£52.7 million), oxycodone (£47.0 million) and fentanyl (£26.5 million) analgesics [45]. However, the breakdown of the estimated cost of opioids used for specific CNCP conditions is not known and remains unclear.

2.2 Management of chronic non-cancer pain

Different types of strategies are used in clinical settings for the management of chronic non-cancer pain. Management options generally include: pharmacological, behavioural medicine, interventional methods, and surgical methods [46]. Multiple approaches are often used for optimal management, depending on the nature of pain being treated and the treatment goals.

In the UK, clinical recommendations have been developed by various organisations such as the National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network, Faculty of Pain Medicine, Royal College of Anaesthetists and The British Pain Society (BPS) for the management of chronic pain [47-50]. This section provides a brief overview of some of the current recommendations.

2.2.1 Pharmacological management

The main ideal goals of pharmacological management of CNCP are to diminish pain and to restore function and quality of life. Pharmaceutical approaches are the most widely used strategies for chronic pain, and analgesics that are frequently used for acute pain are also used in chronic pain. Paracetamol, NSAIDs, antidepressants and anticonvulsants are often recommended and are useful for a number of CNCP conditions.

Paracetamol is known to be amongst the most commonly prescribed analgesics in primary care; however, evidence of its efficacy in chronic pain is limited [51]. Recent evidence published in 2016 by the Cochrane Database of Systematic Reviews reported no significant reduction in pain and function compared to placebo in chronic low back pain and as such, NICE guidelines no longer recommends paracetamol on its own as a first line option for low back pain [52, 53]. Furthermore, although there have been debates about the use of paracetamol in osteoarthritis,

the drug is still recommended as a first line due to evidence of a small superiority effect of pain relief compared to placebo [54, 55].

Most guidelines agreeably conclude a recommendation of non-steroidal anti-inflammatory drugs (NSAIDs) and topical capsaicin pain plasters for most musculoskeletal-related pain conditions [55-58]. For instance, NSAIDs have been shown to be effective in the symptomatic management of rheumatoid arthritis during the initiation of disease modifying anti-rheumatic drugs (DMARDs), where it recommends the use of the lowest possible doses of NSAIDs to be used within the shortest period [57]. While in osteoarthritis, topical NSAIDs are advised ahead of oral NSAIDs [55] .

Similarly, in chronic low back pain, NSAIDs are recommended as a first line option only if non-drug management has proven to be inadequate. However, the use of NSAIDs in general has been recommended with caution due to their potential risk of serious adverse effects [59, 60]. Succinctly, NSAIDs carry a heightened risk of cardiovascular events (CVD) such as myocardial infarction, stroke and heart failure, and may also precipitate renal failure and gastrointestinal bleeding [61]. This makes it a difficult therapeutic option, particularly for specific groups of patients. Although the risk of adverse events with NSAIDS is a group effect, differences exist between the drugs, and this depends on whether the drugs are cyclooxygenase (COX) 1 or 2 selective [62]. Moreover, while the risk of adverse effects increases with dose, there is no increase in effectiveness with higher doses of NSAIDs due to a ceiling effect, which limits their usefulness [63].

Strong clinical evidence exists for the use of antidepressants in the management of neuropathic pain, including diabetic neuropathy and postherpetic neuralgia, and current recommendations

advises the use of antidepressants as first-line analgesics for neuropathic pain [56, 64, 65]. Furthermore, antidepressants have been reported to be effective in decreasing pain in fibromyalgia, and in managing depression and enhancing quality of sleep in chronic pain patients [66, 67].

However, the extent of antidepressants' analgesic effectiveness in managing other types of musculoskeletal conditions such as low back pain is inconclusive and results from clinical trials have been conflicting [68]. Recently, in 2016, NICE updated their guidelines and highlighted that serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants and anticonvulsants should no longer be used in the management of low back pain [53]. This followed on from reviews of recent randomized controlled trials which showed that there was no significant difference in pain relief between antidepressants, anticonvulsants and placebo treatment, and that there were also conflicting results in the reduction of depression with antidepressants in chronic low back pain [69, 70].

Apart from antidepressants, anticonvulsants are also recommended as first-line treatment for neuropathic pain, and their use has been found to be effective in several empirical clinical trials [71-73]. NICE guidelines have updated their recommendations to include newer anti-epileptic drugs (AEDs) such as gabapentin and pregabalin as a first-line treatment for neuropathic pain. This is supported by evidence of randomized controlled trials that show valuable treatment outcomes of AEDs in painful neuropathic conditions [56].

In terms of invasive pharmaceutical modalities such as trigger point injections, botulinum toxin injections and nerve block injections, these have limited supportive evidence in the treatment of chronic non-cancer pain patients and controlled clinical trials of their long-term utility are

lacking [74, 75]. Surgical interventions are not routinely practiced but are recommended in the presence of unresolved neurological deficit, such as herniated disc in sciatica or back pain related spinal deformity [58].

2.2.2 Non-pharmacological management

Non-pharmacological interventions have increasingly become recognised as an important tool in the management of chronic non-cancer pain [76]. The interventions, which are generally classified into physical, cognitive, behavioural and other non-invasive methods, are aimed at restoring posture, mobility, strength and enhance patients' self-efficacy for leading a functional life [77]. While non-pharmacological interventions can be a stand-alone treatment, they are frequently used as adjunct therapies to pharmacological treatment.

Recent research has shown that the application of exercise and physical therapy in the management of chronic non-cancer pain conditions, particularly that of chronic musculoskeletal pain, does not only enhance mobility and reduce the severity of pain, but it also has beneficial effects on cognitive function and actively promotes patients' involvement in pain management, thus increasing self-management [78, 79].

Physical activity is increasingly promoted by various guidelines; for example, NICE recently updated its 2009 guidance on the management of low back pain to include exercise in all its form as an initial step in the management of low back pain, and encourages this to be combined with psychological interventions if there are signs and symptoms of significant psychological impacts [58]. Likewise, NICE's osteoarthritis guidelines state that exercise should be recommended as core treatment irrespective of age, comorbidity, pain severity or disability [55]. The Scottish Intercollegiate Guidelines Network, the British Pain Society guidelines and the

British Geriatrics Society guidelines for chronic pain management also recommend exercise, based on evidence drawn from randomized controlled trials (RCTs) [48, 80]. However, the exact type of exercise intervention that is most effective is less clear, and the subgroup of patients that benefit from the treatment remains to be highly heterogeneous [81].

Cognitive behavioural therapy acknowledges the influence of personal beliefs, psychological state and mood on the response and outcomes of pain and, as such, the intervention aims to alter dysfunctional thoughts and behaviours, and breaks the cycle of a self-defeating attitude [82, 83]. Thus, progresses the patient towards a more pain-adaptive and helpful thoughts for coping. The efficacy of CBT in patients with chronic pain have been assessed in randomized controlled trials (RCTs), and this has been demonstrated to have a small but significant effect on pain and disability, as well as a moderate effect on mood and catastrophizing [82].

However, CBT interventions vary in their format, content and delivery and it is not clear as to which aspect of CBT components, delivery approach and number of sessions are optimal for effective outcomes for different CNCP conditions [84]. Nevertheless, NICE guidelines recommend CBT for managing CNCP conditions such as low back pain, but it has indicated that more evidence is needed to support the intervention in other conditions, such as chronic headache and chronic neck pain [53, 85].

As for other non-invasive interventions such as acupuncture, while evidence shows its effectiveness in the management of migraine and tension headache, the guidelines generally advise its use as a prophylaxis in such conditions. Neither acupuncture nor TENS are recommended for low back pain due to insufficient evidence of effectiveness in randomized controlled trials [53, 85].

2.2.3 Multidisciplinary management

Research has also been increasingly indicative of the benefit of a multidisciplinary approach to the management of chronic non-cancer pain, and this has shown to be effective particularly in chronic back pain [86, 87]. The multidisciplinary approach refers to the partnership of different disciplines to meet patients' different health needs, and this is specifically targeted at patients who have not responded well to a single treatment approach and whose pain is directly or indirectly impacted by a multitude of factors. This approach is most often comprised of separate consultations with specialists in different disciplines before a shared management plan is decided [88, 89]. The effort is aimed at fostering a comprehensive physical and psychosocial approach to patients' pain management to improve quality of life, social functioning, pain severity, and carefully monitor the consumptions of analgesia [89].

Examples of healthcare professionals in a multidisciplinary pain management team include physicians, psychologists, nurses, physiotherapists and pharmacists. The management programme integrates different components of therapies such as physiotherapy, use of medication, patient education, cognitive behavioural therapy and ergonomic training [48]. However, research has not yet unravelled the components of the management that is of particular importance, and it is not clear as to the characteristics of patient groups (e.g. age-group, duration of CNCP and socioeconomic background) that would benefit the most from the care [90].

Both the Faculty of Pain Medicine and the British Pain Society have produced core standards for the provision of pain management services across the healthcare system, which are aimed at healthcare professionals, commissioners and other stakeholders [48, 80]. A report by the Clinical Standards Advisory Group (an independent advisory group to the NHS), published in

2012, indicated that the provision and access of multidisciplinary pain services across the UK varied [91]. Furthermore, the report stated that only 40% of pain clinics in England, and 60% in Wales, met the minimum multidisciplinary standards in terms of the presence of a psychologist, physiotherapist and physician. Some of the variability in chronic pain service provision could be explained by a lack of uniform consensus on the clinical benefits, and there are currently no agreed national standards for the service, which makes the measure of outcomes less feasible [91].

2.2.4 Management challenges

The management of chronic non-cancer pain can be a challenge for several reasons. Studies show that prolonged pain can result in changes in the central nervous system that result in a bolster or exaggeration of pain (hyperalgesia), or the experience of pain from non-noxious stimuli (allodynia) [92-94]. This phenomenon is termed neuroplasticity and arises when neurones in the pain pathway become more sensitive, respond more strongly to stimuli and develop more connections to secondary neurones in the central nervous system [92, 95].

The mechanism ultimately leads to further long-term pain, and in such instances the pain becomes a disease and not only a symptom. Furthermore, the sole use of peripheral or spinally active therapies, which are the current pharmacological conventional interventions, as described earlier, become less likely to be useful in addressing pain that is maintained by central sensitization [96]. An example of this in practice is with chronic conditions such as arthritis (rheumatoid and osteoarthritis); here, central sensitization happens over time and in response to on-going joint pathophysiology which results in raised pain and tenderness that also occurs away from the area of joint damage [97, 98]. A further example is idiopathic pain, which is a condition with unexplained medical causes but with signs of an underlying mechanism of

central sensitization. Such a condition includes chronic back pain with unidentified causes, fibromyalgia and non-traumatic neck pain [14]. Many details of how such pain conditions occur, and why a relative proportion of patients develop chronic pain with unknown pathology, are not well understood. Nevertheless, the challenge in such cases is that it becomes difficult to direct existing treatment modalities of known mechanisms of action to the condition(s) [99].

It is also generally unwise to underestimate the extent to which psychological factors such as catastrophizing, fear and social factors play a central role in influencing chronic pain-related outcomes, such as pain severity and disability [100, 101]. What is known from current research is that psychological influences of pain makes it difficult to distinguish between the extent of pain that is caused by the organic components of pain and the extent of pain inferred by psychosocial elements, and hence this makes it problematic to direct existing treatments accordingly [102, 103]. Another cited challenge in pain management is the objectivity in measuring the experience and intensity of pain due to the subjective nature and idiosyncratic expression of pain; yet, self-reporting of pain remains the "gold standard" assessment tool used for measuring pain [104]. Self-report measures of pain are divided into two types of tools: single-dimension and multidimensional assessments [105].

Single-dimension assessment involves asking patients to rate their pain on scales (numeric or visual) that can range from 0 to 10, whereas the multidimensional tool evaluates behavioural and emotional aspects of pain. Although the reliability of the scales used in practice has been shown to be valid, pain intensity ratings are limited by the extent of information they can provide, for example the pathophysiological nature or anatomic consequence of pain are not captured [106].

Several physiological variables have been suggested as additional objective biomarkers of pain, such as skin conductance and heart rate [107, 108]. However, these markers are not necessarily or directly linked to pain and may not be a viable option as a surrogate measure of pain [109-111]. Newer approaches have concentrated on neuroimaging methods such as functional MRI, which generates high resolution imaging of the brain regions that are suspected to be involved in pain-related activity including pain severity. However the technology is not yet able to quantitatively indicate the likely progression of patients' pain at the acute phase and research efforts still continues in this area [112].

Moreover, a caveat to this is that even in the relative measure of pain intensity, the gross reliance on patients' pain intensity ratings as a guide for a therapeutic treatment option and a measure of treatment success as explained by Ballantyne JC et al. (2015) is not necessarily an optimal practice. This is due to the multifactorial variables involved in pain, which could go beyond the measure of pain intensity [113].

Furthermore, assessment of elderly patients with chronic non-cancer pain using self-reported tools can be challenging [114]. A large percentage of older adults develop changes in cognition, mobility and sensory perception, which can influence their capacity to communicate about their pain or estimate pain intensity. This can possibly result in an under or over-estimations of pain within this subgroup [114]. A further challenge is that adequate management of moderate to severe chronic non-cancer pain can prove to be difficult with non-central acting analgesics. Non-steroidal anti-inflammatory drugs and paracetamol have an analgesic ceiling effect and can be toxic at high doses [63]. This can be a concern of its own in general but also more specifically in the elderly patients and in patients with serious comorbidities.

Moreover, while a group of chronic non-cancer pain patients may get better and respond well to traditional first line analgesics (NSAIDs, paracetamol, aspirin antidepressants, antiepileptics) or non-pharmacological modalities, another group may respond poorly over long periods and their persistent pain may not improve [115]. In such instances, the use of opioids, particularly stronger forms of opioids, long-term may seem like a desirable option in moderate to severe chronic non-cancer pain. However, prolonged use of opioids in non-cancer pain is not without considerable contention, and their safety and effectiveness is at the heart of the debate in the literature [116]. This is further examined in the following section.

2.3 Opioids in chronic non-cancer pain: a review of efficacy and safety

Opioids are recognized as an important therapeutic class, and historically they have contributed to the management of many ailments [117-119]. They produce analgesia through their complex interactions with endogenous receptors situated in the central nervous system (CNS), gastrointestinal tract and, to a lesser extent, in the peripheral tissues [120]. Opioids act on four types of receptors: the Mu (μ), Kappa (κ), Delta (δ), and Sigma (δ) receptors. The activation of Mu-receptors generates supraspinal analgesia and euphoria, but also respiratory depression, urinary retention, sedation, constipation and dependence. Activation of Kappa receptors produces spinal analgesia, dysphoria, sedation and respiratory depression. Similarly, stimulation of Delta receptors yields supraspinal and spinal analgesia, respiratory depression, urinary retention and dependence. Whereas, the activation of Sigma receptors may induce physiological side effects such as hypertonia (abnormal muscle reflexes), tachycardia and mydriasis (dilated pupils) [120].

Opioids are categorised according to their actions on the receptors as agonists (oxycodone, morphine, fentanyl), partial agonists, mixed agonist-antagonists (buprenorphine, butorphanol,

nalbuphine), and antagonists. The division describes the differing degrees of receptor binding (affinity) and the outcome response from the interactions (efficacy) [120] (Table 2-2). Recently in 2010, opioids were further classified according to their strength of activity into weak and strong opioids [121].

Amongst strong opioids, notable differences exist in their pharmacology, including analgesic effect and adverse events. Full strong opioid agonists such as morphine, fentanyl and oxycodone fully stimulate opioid receptors, and produce their effect linearly with increasing dosage. As a result, they also have the highest potential of abuse and dependence. Partial agonists, such as buprenorphine on the other hand, have an inferior receptor affinity and possess a ceiling to their effect compared to full agonists [122].

Table 2-2 Opioid classifications

Drug	Classification	Receptor activity
Weak opioids		
Codeine	Agonist	Mu
Dihydrocodeine	Agonist	Mu
Strong opioids		
Morphine	Agonist/Weak agonist	Mu/Kappa
Oxycodone	Agonist	Mu
Buprenorphine	Partial agonist/Antagonist	Mu/Kappa
Diamorphine	Agonist	Mu
Strong opioids		
Hydromorphone	Agonist	Mu
Pethidine	Agonist	Mu
Fentanyl	Agonist	Mu
Methadone	Agonist	Mu
Alfentanil	Agonist	Mu
Remifentanil	Agonist	Mu
Tapentadol	Agonist	Mu
Tramadol	Agonist	Kappa

Note: modified from Trescot AM et al. (2008)[120].

(Continued) Table 2-2 Opioid classifications

Drug	Classification	Receptor activity
Strong opioids		
Naloxone	Antagonist	Delta
Naltrexone	Antagonist	Delta
Nalmefene	Antagonist	Delta
Pentazocine	Agonist/Antagonist	Delta
Meptazinol	Partial agonists	Mu-1

Note: modified from Trescot AM et al. (2008)[120].

Opioids are primarily used to treat pain related to acute, cancer and end of life palliative care, and this has been a practice in clinical settings for centuries [123-127]. In these conditions, the durations of symptoms are often finite and short lived, and treatment efficacy with opioids is extensively documented and evidence-based [128, 129]. While the use of opioids short-term is of no dispute, their use in chronic non-cancer pain is a recent phenomenon in the history of opioid prescribing, and there are limitations in the evidence that demonstrates effectiveness of opioids over prolonged periods in chronic non-cancer pain, and further issues under discussion relate to potential serious adverse effects, including problematic use such as dependence and abuse [130-136]. Thus, to gain a clear understanding of the evidence-based information available on the use of chronic opioid therapy in CNCP, and to gain an enhanced understanding of the areas of knowledge uncertainty, this section aimed to evaluate the current state of evidence from the literature. A structured review was undertaken and divided into two parts; the first part include a critical review of studies that covered evidence of effectiveness of long-term opioid therapy in non-cancer pain, and the second part of the section discusses safety of opioid use long-term in non-cancer pain, before a final summary of the evidence and gaps in the literature is presented.

2.3.1 Review method

2.3.1.1 Search strategy

The literature was systematically searched for studies describing the efficacy and safety of opioid use long-term in non-cancer pain, using MEDLINE (1996-2016), CINAHL (1996-2016), the Cochrane Central Register for Controlled Trials (through to 2016), the Cochrane Database of Systematic Reviews (through to 2016) and the PsychoInfo (1996-2016) databases. A broad search strategy was used in the databases, which combined medical subject headings (MeSH terms, exploded) and free texts words, which is available in (Appendix 2). The electronic search was supplemented by additional studies from reference lists not identified through the electronic search. All identified citations were imported into Endnote (X7) and considered for inclusion. The literature search was initially conducted in 2013 and updated in 2016.

2.3.1.1.1 Inclusion and exclusion criteria

Titles and abstracts of retrieved citations were screened against a set of predefined Population Intervention Comparison Outcome eligibility criteria and full copies of the studies thought to meet the inclusion criteria were obtained and re-examined (Table 2-3). Studies were included if: (a) the study participants were 18 years and over, (b) the study sample had chronic non-cancer pain (defined as pain persisting longer than 3 months), (c) study participants were prescribed opioids either orally, transdermally and buccally for at least 12 weeks or over (opioid administered intravenously, intrathecally, intraspinally, intramuscularly and subcutaneously were excluded because these are less likely methods for the long-term management of chronic pain), and (d) the study outcomes included measures of efficacy and safety, such as pain relief/pain intensity reduction, improved physical functioning, quality of life and occurrence of adverse effects. The inclusion criteria are expanded in (Table 2-3).

The examination of ≥12-week treatment threshold was selected because this has been previously defined as prolonged therapy of opioids [137]. This is based on the notion that a ≥90-day treatment time-point is less likely to indicate the management of acute conditions, and treatment is more likely to be for chronic pain [137].

Table 2-3 Inclusion and exclusion criteria

TYPES OF STUDIES
Inclusion criteria - English language - Original full studies - RCTs, observational, case reports, systematic reviews, meta-analysis Exclusion criteria - Non-English language - Grey literature / not published in a peer -reviewed journal - Dissertations /theses - Proceedings - Published abstracts
TYPES OF PARTICIPANTS
Inclusion criteria - Adults (>18 years) - Diagnosed with a chronic non-cancer pain condition (defined as pain persistent for longer than 3 months) Exclusion criteria - Children (<18 years) - Pregnant women - Persons with active cancer - Persons in need of palliative care or end of life care - Persons with acute pain (e.g. post-surgical pain, labour pain)
TYPE OF INTERVENTION
Inclusion criteria - Any opioid (agonist/partial agonist/antagonist) administered by the oral, transdermal, buccal route - Duration of opioid use ≥90 days (≥12-weeks) was the main interest since this duration has been defined as long-term use.

(Continued) Table 2-3 Inclusion and exclusion criteria

TYPE OF INTERVENTION
Exclusion criteria - Opioids administered via the intravenous, intrathecal, intraspinal, intramuscular and subcutaneous route - Opioids prescribed for the treatment of substance misuse/abuse
TYPE OF COMPARATORS
Inclusion criteria - Opioids compared to placebo - Comparison between opioids - Comparison between opioids and non-opioid analgesics
TYPES OF OUTCOME MEASURES
Inclusion criteria Efficacy - Pain relief or pain intensity (as measured e.g. using rating scales) - Physical functioning - Emotional functioning - Quality of life (including sleep quality) Safety - Adverse effects (e.g. harm to cardiovascular, respiratory, central nervous, gastrointestinal system) - Aberrant drug-related behaviour - Overdose - Mortality Exclusion criteria - Pharmacokinetic/pharmacodynamic outcomes

Individual randomized controlled trials and observational studies from the various databases which met the inclusion criteria, but which had already been reviewed in the included systematic reviews, which were extracted from the Cochrane Database of Systematic Reviews, were excluded to prevent duplications in evaluating studies.

2.3.1.2 Quality assessment

The quality of studies was evaluated using different assessment tools to gain an overview of the quality of the reviewed studies. Randomized controlled trials (RCTs) were evaluated using predefined criteria developed by the Cochrane Back Review Group [138]. This consist of 11 domains, which are relevant to internal validity (such as randomization, blinding, etc.) and outcome measures, each domain are rated as positive (Yes), negative (No) or inconclusive (Appendix 3). A total sum score of positive ratings of 6 or higher indicate a lower possibility of bias.

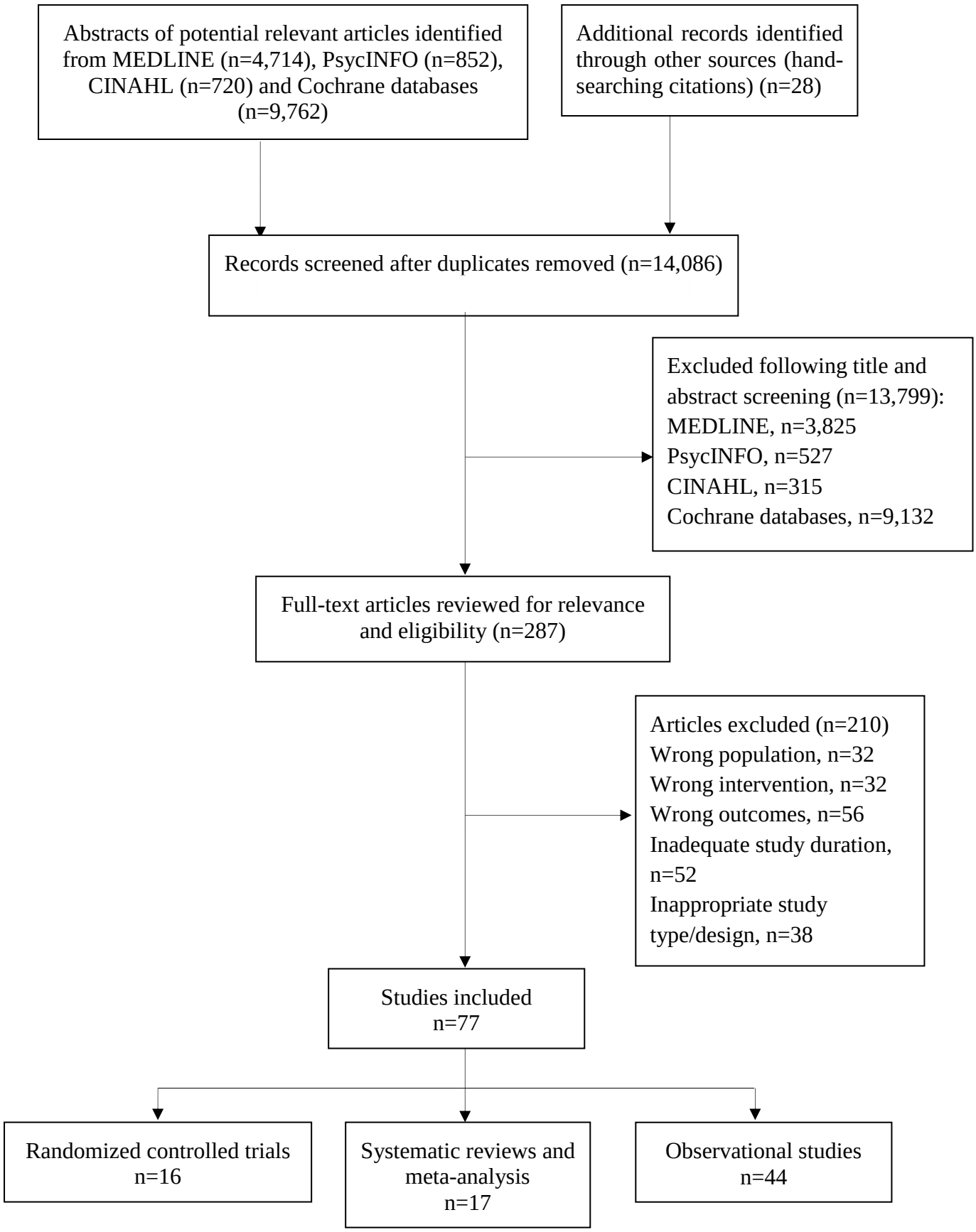
Systematic reviews of RCTs on the efficacy and safety of opioids in chronic non-cancer pain on the other hand were evaluated using Oxman and Guyatt's method. This is based on 10 assessment criteria, which include the evaluation of the inclusion criteria, study selection, study assessment, data synthesis and conclusions [139]. Each of the criteria is rated as Yes, No or Unclear, and an overall score of ≥7 affirm minimal flaws or bias (Appendix 3).

Non-randomized controlled trials, such as that of observational studies, were assessed using the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) assessment method developed by the Cochrane Bias Methods Group and the Cochrane Non-randomized studies Methods Group [140]. The tool assess studies based on 7 domains, which include confounding, selection of subjects into the study, measurement of interventions, withdrawal from interventions, missing data, measurement of outcomes, and the overall findings (Appendix 3).

2.3.1.3 Results of the search strategy

The electronic database search (and hand-searching for reference) generated 14,086 records after the removal of duplicates. Following the review of titles and abstracts, 287 citations were retrieved for full-text review (Figure 2-1). The most frequent reasons for study exclusion included: the duration of opioid use, e.g. short-term use of less than 12 weeks; the outcome measures evaluated, e.g. evaluation of opioid efficacy/safety in breakthrough pain; the use of parenteral opioids; or the evaluation of opioid use in cancer pain or in children. A total of 77 studies that assessed the efficacy and safety of long-term opioid therapy in chronic non-cancer pain were found to meet the inclusion criteria; of these: 16 citations were randomized controlled trials (most with an open-label follow up), 17 were systematic reviews and 44 were observational studies. A summary of the findings from the individual RCTs and systematic reviews are tabulated in Appendix 4 and Appendix 5.

Figure 2-1 Flowchart diagram of citation screening and study selection process



2.3.2 Clinical efficacy

The available evidence generated on the use of opioids for chronic non-cancer pain over the years have been scarce, highly variable and at times contradictory in generating firm conclusions on the use of long-term opioids in chronic non-cancer pain. This section will highlight a description of some of the findings from the reviewed literature on the efficacy and safety of opioids in chronic non-cancer pain over a use of ≥12 weeks (or ≥90 days).

2.3.2.1 Randomized controlled trials

Evidence generated from randomized controlled trials (RCT) is regarded as the highest level for assessing efficacy and safety, primarily because of the minimal risks of bias and systematic errors [141]. This is mainly achieved through the random nature of allocating interventions to the study subjects, which ensures a reduction in allocation bias and ensures participants' characteristics are less likely to be related to the outcome(s) of the intervention. Thus, also reducing bias from confounding. Moreover, RCTs can rigorously determine the effect size of a treatment in relation to either placebo or other interventions.

Different types of RCT designs exist; however, the most common trial designs conducted to investigate opioid use in CNCP have been parallel designs, crossover designs, single blind trials, double-blind trials and open-label trials. A brief description of the types is provided prior to reviewing the trials.

Parallel trials: participants are separated into two parallel groups where each group receives only one treatment intervention (i.e. therapeutic or control group) [142].

Cross-over trials: unlike parallel-group trials, all participants in cross-over trials receive all

interventions in a sequential manner, usually with a washout period; thus, each patient acts as their own control [142].

Open-label trials: are designed so that interventions are not masked/blinded and patients, clinicians and care providers know who is receiving the therapeutic intervention and the control treatment [143].

Single-blind trials: are trials in which only the patients are blinded and unaware of the type of intervention received [143].

Double-blind trial: are trials where treatment allocations are blinded for all parties involved (patient, clinicians, and care providers) [143].

In a 12-week double blind placebo controlled randomized trial, buccal buprenorphine's efficacy and safety was assessed in patients with moderate to severe chronic low back pain that had lasted for 6-months or more [144]. The study was divided into a 2-week screening phase, an 8-week titration phase, a 12-week double blind randomized treatment phase and a 2-week follow-up phase. At the beginning of the titration period, all the patients who met the inclusion criteria (n=749) had all their prior analgesic treatment ceased. They were subsequently initiated with buccal buprenorphine at a progressively increasing dosage, from 75µg once daily up to 450µg twice daily subject to reaching a stable patient analgesic response. Only patients who had reached the stable optimal dose of ≥150µg twice a day for more than 2 weeks in the titration phase were entered into the randomized double-blind phase. Here, an equal number of subjects received buccal buprenorphine or placebo for 12 weeks. Treatment efficacy was assessed from baseline to week 12 and effectiveness was defined as achieving ≥30% or ≥50% reduction in

the numerical rating scale (NRS) score and tolerable adverse effects. Out of 749 patients studied, 38.3% were discontinued at the titration phase due to intolerable adverse effects and the experience of inadequate pain relief. The remaining 61.7% (n=462) entered the double-blind phase, but a further 6.1% of patients from the buccal buprenorphine-treated group and 3.0% from the placebo group discontinued the interventions during the 12-week treatment phase.

At the end of the 12-weeks, a significantly higher number of patients treated with buccal buprenorphine (63%) than the placebo group (47%) experienced ≥30% level of pain reduction, decreasing the mean pain intensity from moderate or severe to mild. However, there was no significant difference detected in the number of patients experiencing ≥50% pain reduction between the two groups (p = 0.0754) at the end of the trial.

Miller K et al. (2014) also investigated buprenorphine, but in its transdermal formulation, in patients with moderate to severe chronic low back pain in a 12-weeks randomized double blind placebo controlled trial [(145)]. The trial sought to evaluate the impact of buprenorphine 7-day transdermal patch on patients' daily physical activities such as lifting, bending, working and quality of sleep. Five hundred and forty-one (n=541) patients met the study inclusion criteria and were entered in an initial run-in phase for ≤27 days. During this time, patients received a weekly-titrated dose of buprenorphine transdermal patches, and patients with an established minimum tolerable dosage were entered in the double-blind placebo trial. A total of n=363 completed the double-blind phase with n=166 randomized to the buprenorphine transdermal patch and n=197 on placebo for 12 weeks. Activities of daily living (ADL) was measured against WHOs' low back pain domains of the International Classification of Functioning, Disability and Health (ICF), which defines a core set of activities necessary for daily living.

Sleep was measured using a 12-item criteria (MOS-SS), which includes self-reported measure of sleep adequacy, sleep disturbance and somnolence (state of sleepiness).

At the end of the 12-weeks, there were statistically significant differences in the performance of certain ADL such as sleeping (p=0.0114), bending (p=0.0214) and lifting (p=0.0100) in the buprenorphine-treated group compared to placebo. However, there was no statistical significant difference reached in the capacity for walking a mile, walking for several hundred yards and walking without pain between the two groups.

In a different double blind placebo controlled trial, Hale ME et al. (2007) assessed the efficacy of oxymorphone hydrochloride extended release (OPANA ER) over a period of 12-weeks in patients with moderate to severe chronic low-back pain [(146)].

Two hundred and fifty (n=250) patients participated in an initial 3-7 days titration period in which patients received OPANA ER prior to randomization, and had their dose adjusted to attain pain relief. Only one hundred and forty-three (n=143, 57%) patients were entered in a double-blind randomization treatment of either continuation of oxymorphone ER (n=70) or placebo (n=73). The reduced participation was due to treatment discontinuation due to adverse effects that had occurred at the titration phase. Pain intensity was assessed using a visual analogue scale (VAS). Following randomization, only 49 of the 70 OPANA ER patients and 18 of 73 placebo-treated patients completed the 12-week trial, and many discontinued within the first 10 days of the trial mainly due to lack of efficacy and adverse effects. Patients on placebo had a significant (p<0.0001) increase in pain intensity (mean change from baseline=31.6, sd=2.9) compared to OPANA ER (mean change=8.7, sd=3.0). Patients on

OPANA ER had a stable analgesia throughout the 12-weeks and lower pain intensity than placebo; however, this did not decrease further with prolonged usage.

Opioid use in chronic non-cancer pain has also been examined in several open-label follow-up studies. Although these are less rigorous than blinded randomized controlled trials, they provide further evidence on opioid use over prolonged periods of greater than 90 days (>3 months).

Arora S et al. (2014) included 395 patients with moderate to severe chronic non-cancer pain in a 12-month open-label trial in which oxycodone-naltrexone extended release were received [(147)]. The majority of the included patients discontinued treatment mainly due intolerable adverse effects (31.65%, n=75) and lack of efficacy (15.61%, n=37). Pain intensity was measured as the mean change in pain score from baseline using a 0-10 numerical rating scale (0=no pain and 10=worst pain imaginable) and only a small improvement in pain score was observed for the participants studied (mean change from baseline; -1.3±2.32 at month 12). An upward dose adjustment of oxycodone/naltrexone ER was found to be required following initiation and over time; the average daily dose at baseline was 38.6mg, and at month 11 this was 76.2mg.

Patterns of dose-escalating with opioid use was also found in an open-label follow-up study of a randomized controlled trial, which was designed to assess differences in efficacy and tolerability between extended release oxycodone/naloxone, oxycodone and morphine for a period of 12-weeks [(148)]. Overall, n=901 patients with chronic low-back pain received treatment in 1:1:1 ratio. However, 35.5% of patients ceased to continue the use of the medications over the study period due to the emergence of intolerable adverse effects (morphine: 25.0%,

oxycodone 24.7%, oxycodone/naloxone 7.3%) and/or inadequate effectiveness (morphine: 31.0%, oxycodone: 31.3%, oxycodone/naloxone: 21.3%).

The trial noted a substantial increase in overall mean dosage in morphine equivalent (MEQ) from an average of 28.7±10.8mg at the start of the trial to 107.8±37.2mg at the end of the trial. The average morphine equivalent dose use at the end of the trial was found to be higher with oxycodone/naloxone (112.9±34.2 mg, 95%CI: 109.5–116.3) than either oxycodone (106.6±37.4 mg, 95%CI: 102.9–110.3) or morphine (103.8±39.3 mg, 95%CI: 99.9–107.7). Concurrently, at the end of the 12-week treatment decreased pain intensity, improved sleep and quality of life were experienced more so with oxycodone/naloxone than with oxycodone and morphine.

Meanwhile, in a prospective randomized longitudinal study, Mitra F et al. (2013) found that a very small proportion of the originally assessed non-cancer pain patients using transdermal fentanyl and transdermal buprenorphine had sustained pain relief beyond 6 months [(149)]. Forty-six (n=46) patients with persistent non-cancer pain lasting more than 6 months and who were not receiving opioid treatment were enrolled. Patients were randomly allocated to one of two treatments; either with transdermal fentanyl or buprenorphine patches initiated at a minimum dosage of 12 μg/hour and 5 μg/hour respectively and titrated within 4 weeks, according to response. The outcome measures assessed included pain levels using a (0-10 scale) visual rating scale, physical functioning, sleep quality and mood using a SPAASMS rating score (0=very good, 1=good, 2=fair, 3=nil/low/poor) at 3-months intervals.

In total, 16 of the 46-patients continued treatment for 12-months and almost an equal number of patients on either treatment discontinued due to adverse effects or lack of pain relief (41%

of the buprenorphine group and 37.5% of the fentanyl). Significant pain improvement and a reduction of 3 points in the visual analogue scale were observed at month 3 in 50% of patients using buprenorphine and 42% of patients using fentanyl. A greater equipotent dose of fentanyl was needed to achieve similar pain relief to buprenorphine, and a greater number of patients using fentanyl (57%) compared to buprenorphine patients (31%) required additional analgesics to control pain from months 3 onwards. At the end of the 12 months, only 11% of patients continued to have pain relief. In addition, no significant group differences was found for either function or mood improvements [(149)].

Over recent years, multiple systematic reviews have been published that have examined RCTs on the efficacy of opioids in chronic non-cancer pain over several months. One review published in 2007 investigated some of the earliest randomized controlled trials [(150)]. The review, which only included patients with chronic low back pain (>6 months), found 11 of the 38 studies to be randomized controlled trials, in which 4 where open-label randomized controlled trials with duration of up to 16 weeks.

The review found inconsistent evidence in support for opioids and meta-analysis showed a combined standard mean difference (-0.199, 95%Cl: -0.49 to 0.11, p= 0.136) that indicated a non-significant decline in pain in patients treated with opioids compared to non-opioids or placebo. The review concluded a limited efficacy of opioids in chronic back pain compared to placebo or active controls of up to 16 weeks [(150)].

A similar conclusion was drawn by Kalso E et al. (2004), who reviewed 18 randomized double-blind placebo-controlled trials that assessed strong opioids' (fentanyl, hydromorphone, methadone, morphine, oxycodone and oxymorphone) efficacy and safety in chronic non-cancer

pain [135]. Eleven (n=1025 patients) of the trials assessed oral opioids in patients with neuropathic, musculoskeletal and mixed pain over 4 to 8 weeks, and reported a 30% reduction in pain intensity in neuropathic and nociceptive pain.

However, only six (n=388 patients) of the initial double-blind placebo trials had an open-label follow up and assessed treatment over duration that ranged from 6 months to 24 months. At the end of the 24-months, more than half of the patients (56%) were found to have ceased treatment due to adverse effects or inadequate analgesic efficacy, and only a marginal fraction of patients continued treatment long-term. Based on the insufficient results and due to methodological limitations of the open-label follow-up studies, long-term efficacy of opioids could not be substantiated by the author.

Following Kalso's review, and in the subsequent years, a larger review was carried out by Furlan A et al. (2006) to assess the efficacy and safety of opioids (codeine, morphine, oxycodone, tramadol and propoxyphene) in patients with a wide range of CNCPs that included nociceptive, neuropathic, fibromyalgia and mixed nociceptive and neuropathic pain [134]. The review included 41 randomized controlled trials (n=6019) with durations that ranged from 1 to 16 weeks.

Effectiveness in the form of improved pain scores and physical function as measured by a standardized mean difference (SMD) procedure was reported in patients with nociceptive, neuropathic, and fibromyalgia compared to placebo. Strong opioids (oxycodone and morphine) reduced pain (SMD –0.34, 95%CI –0.67 to –0.01) more than weak opioids and non-opioids, whereas non-opioid analgesics were more effective in enhancing function (SMD –0.34, 95%CI –0.67 to –0.01). A great number of patients dropped out of the trials and up to 30% of the drop-

outs were primarily due to a lack of sufficient pain relief and 10% were due to the experience of intolerable side effects.

Furlan A et al. (2006) concluded that long-term efficacy with transdermal opioids could not be concluded since only two trials assessed long-term use, which was inadequate for meta-analysis. For oral opioids, the review specified that there was weak evidence of pain reduction over 6 months, and heterogeneity in the level of pain relief experienced was noted in the trials [(134)].

In a latter review, Noble M et al. (2010) included 26 uncontrolled case-series studies (including open-label continuation of RCTs) and 1 randomized controlled trial (n=4893 in total) that studied the effectiveness and safety of opioid use for at least 6-months in various chronic non-cancer pain disorders [(151)]. Participants had mostly nociceptive, neuropathic or mixed nociceptive and neuropathic pain of moderate to severe intensity at baseline. Treatment discontinuation due to adverse effects and inadequate pain control was found to be high, and considerably higher with the use of oral and transdermal opioids. Treatment termination due to adverse effects with oral and transdermal formulations occurred in 22.9% (95%CI: 15.3% to 32.8%) and 12.1% (95%CI: 4.9% to 27.0%) of participants respectively. Inadequate pain control occurred in 10.3% (95%CI: 7.6% to 13.9%) of patients using oral formulations and 5.8% (95%CI: 4.2% to 7.9%) in patients treated with transdermal preparations.

The review concluded that a moderate pain reduction from baseline was plausible; however, due to the high attrition rate and high level of heterogeneity between the reviewed studies, the average amount of pain reduction could not be quantified. Moreover, the author concluded that due to the low internal validity of the reviewed studies, results were based on weak evidence.

There were also inconclusive results regarding quality of life and functional improvements due to inadequate data for analysis, and the review reported a 0.27% occurrence of addiction and abuse.

A more recent systematic review, published in 2015, reviewed long-term opioid efficacy in open label extension studies of randomized controlled trials with duration of ≥26 weeks [152]. A total of eleven open label studies were reviewed with an overall of 2,445 patients with nociceptive pain (back pain, osteoarthritis) and neuropathic pain (radiculopathy, polyneuropathy). The studies' follow-up period ranged from 26 to 108 weeks (median: 26 weeks). Four of the studies investigated oxycodone, two tramadol, and one study each assessed the use of buprenorphine, hydromorphone, morphine, oxymorphone and tapendalol.

Only a third (28.5%) of the initially randomized patients completed the open label follow-up, and a substantial proportion of patients (16.8%) withdrew due to adverse effects or insufficient analgesia (4.9%). At the end of the follow-up period, there was no significant improvement in pain (p=0.50) detected. Furthermore, during the open-label period, 0.08% of deaths were recorded and in one study, 5.7% of patients showed aberrant drug behavior at the end of the follow-up [152].

With regard to efficacy of different opioid formulations, Chou R et al. (2003) examined 16 randomized controlled trials (n=1427) and 8 observational studies (n=1190) that compared pain relief and function of longer acting opioids (such as fentanyl, LA morphine, LA oxycodone, LA dihydrocodeine and LA codeine) with short-acting preparations in patients with chronic non-cancer pain [153]. The studies, which ranged in treatment from 5 days to 6-weeks, were highly heterogeneous in design, population, setting, treatment dose, duration, and in the

assessment mode of outcomes. The majority of the studies did not conduct head-to-head comparisons, and thus provided scant evidence to suggest differences in effectiveness and safety between the formulations. Other crucial outcomes, such as function, were less well reported and remain inconclusive.

With no previous reviews focusing on older patient populations, Papaleontiou M et al. (2010) included and reviewed 6 trials that examined efficacy of opioids within a sample group of >65 year olds [154]. Three trials compared tramadol with placebo and three compared oxycodone, morphine and oxymorphone with placebo, all in patients with osteoarthritis. The trials had a follow-up period that ranged from 14 days to 12 weeks, and although a level of pain reduction was identified, a significant number of patients reported adverse events with opioid use.

2.3.2.2 Observational studies

Observational research such as cross-sectional, cohort, case-control and case studies, although of a lesser quality than randomized controlled trials in assessing the efficacy of opioids, make up the rest of the evidence available in providing information on long-term use of opioids in non-cancer pain.

Earlier observational studies investigating opioid use have been case-reports and case-series [155-157]. These studies have generally reported satisfactory reduction in pain with a non-escalating opioid dose, and with minimal risk of addiction reported. Gardner-Nix JS et al. (1996) conducted one of the earlier case-series studies which described 5 cases of patients maintained on long-term opioids [155]. Three of the included patients were suffering from low-back pain and the remaining two had pain of the groin. Following a trial of various opioid use, patients with low back pain (n=3) were maintained on oral methadone over 3, 5 and 8 months

and reported adequate pain relief (pain rating of 2 and 4 in 0-10 NRS) as well as quality of life, with no dose escalations over the maintenance period, but with side-effects encountered. Patients (n=2) with groin pain on the other hand responded poorly to methadone and gained pain relief with fentanyl patch and long-acting hydromorphone, and where stabilised on a fixed-dosage regimen following titration for months. Despite the study's small sample size and no robust measure of comparative therapies, the author concluded that opioid maintenance therapy, particularly that of methadone, could be effective in a selected patients with non-cancer pain.

Conversely, Taylor and colleagues (2000) carried out a retrospective cohort assessment of 59 patients with chronic pain managed with methadone long-term (average use =18.4 months) [(158)]. Fourteen patients were still on treatment (ON group) during follow-up, n=26 withdrew (OFF group) and 19 were lost to follow-up. In the OFF group, n=6 were non-adherent to treatment regimen, n=8 did not achieve adequate pain relief and n=12 experienced intolerable adverse effects. An overall trend of dose escalations to achieve adequate pain relief were identified for almost all patients from an initial average daily dose of 22.9mg±5.8 to 30.7mg±11.7 at the end of follow-up. This suggested that long-term opioid use in the study sample was accompanied by a degree of dose increase.

Similarly, Macey TA et al. (2011) conducted a cross-sectional study to examine long-term opioid prescribing amongst Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans with moderate to severe (≥4 in 0-10 numerical rating scale) chronic non-cancer pain (non-cancer pain >6months) [(159)]. Of the 762 patients examined, 64% were prescribed opioids, 59% were on short-term opioid therapy (≤90 days/year) and 41% were on long-term treatment (>90days/year). Prescribing was examined within a 12-month period, and long-term users were

found to require greater opioid doses than short-term users; the average morphine equivalent dose for short-term users was 1.7 to 180 mg per day and in long-term users this was 5 to 322 mg per day.

In terms of treatment outcomes, one of the largest cross-sectional studies on long-term opioid use was conducted by a group of Danish scientists. Eriksen and colleagues (2006) used the Danish central personal register and withdrew a random sample of n=16,684 individuals and asked them to participate [160]. Of these, n=10,066 patients with chronic non-cancer pain (non-cancer pain >6 months) met the inclusion criteria for an interview and completed a self-administered postal questionnaire. Patients were categorised into two groups: a pain group and a control group. Data on patients' opioid use were obtained through the questionnaire, and treatment outcomes such as patients' pain relief, self-rated health, extent of bodily pain, quality of life, and physical and social functioning were ascertained. The measures were compared between opioid users and non-opioid users.

Of the total study sample, n=1,906 (19%) were in the pain group and a third of them used analgesics, of which 12% used opioids, 3% used strong opioids and 9% used weak opioids. Opioid users compared to non-opioid users were more likely to report severe/very severe pain, suggesting that treatment did not alleviate pain. Opioid users also reported worse self-rated health, poorer quality of life, reduced physical functioning (OR: 1.55) and an inability to work (OR: 0.37). Although the study's findings may be interpreted as opioids being less useful for chronic non-cancer pain, the authors discussed that the findings could have been affected by a number of confounders [160].

Nevertheless, a number of epidemiological research have echoed similar findings, and have found no or little sustained improvement in outcomes of pain relief, physical and mental

function, as well as work and overall treatment satisfaction, in patients receiving opioids long-term with various chronic pain conditions including spine, back pain, headache and neck pain [161-167].

However, a few recent cohort studies have evaluated self-reported function and quality of life with chronic opioid therapy in non-cancer pain patients and reported improvements in both outcomes [168-171]. Distinctively, the studies were mostly carried out in single practice settings or in multidisciplinary pain care settings, which could have influenced the generalizability of the results generated. For instance, Peng P et al. (2008) studied the outcomes in pain relief, function and quality of sleep of a group of chronic pain patients treated with methadone over an average of 11-months in a tertiary multidisciplinary pain management centre [172]. Patients were managed by various specialised physicians (including anaesthesiologist, neurologist, pain and addiction specialist) and a clinical nurse.

The specialist physicians conducted the initial clinical assessments (including psychosocial assessments and the effect on pain), screened the patients to identify appropriate candidates for methadone therapy and carried out continual regular close monitoring upon initiation of treatment and thereafter. A clinical nurse provided further assistance in the screening of patients by conducting urine drug-testing for addiction, aiding the provision of patient educational training and ensuring the establishment of opioid agreement contracts.

One hundred (n=100) patients were initiated with methadone and stabilised on an average dose of 42mg/day (range: 4-190mg/day). Participants were mostly suffering from back or leg pain (34%), pelvic or hip pain (20%) and headache or migraine (14%). One in three of the patients required supplementary opioids to manage short-term exacerbation of pain, of which a majority

(94%) were prescribed short-acting opioids, and they were limited to a maximum use of 4 doses in 24 hours as per advised. Pain relief, which was measured using a numerical verbal rating scale, improved in 72% of patients (from 7.2±1.7 to 5.2±2.5, $p< 0.0001$), physical function improved in 60% and sleep in 54% of patients. However, more than a third of patients (35%) discontinued treatment mainly due to insufficient efficacy (37%), side effects (23%), or a combination of both (26%). Moreover, despite the strict selection procedure, the cautionary initiation of treatment, and continuous patient support and monitoring, opioid treatment ceased in 2% of patients due to aberrant drug-related behaviour.

2.3.3 Safety

Invariably, all opioids are associated with adverse effects; approximately 50% to 80% of patients in clinical trials encounter at least one adverse effect and, as discussed earlier, opioid-related adverse effects result in high attrition rates and the inability of patients to continue treatment [135, 173].

2.3.3.1 Immediate and long-term harms

Adverse effects known to occur close after the initiation of opioids include: constipation, nausea, vomiting, pruritus, delayed gastric emptying, sleep disturbance, pyrexia, cognitive impairment, dizziness, somnolence and sedation [173-176]. Candiotti and Gitlin (2010) conducted a review to examine the impact of opioid-related adverse effects on the treatment of chronic non-cancer pain patients [177]. They identified that most patients experienced side effects linked to the gastrointestinal and nervous system, with constipation, nausea, and somnolence being the most common cause of premature withdrawal from prolonged treatments. Similarly, a cohort study by Jonsson T et al. (2011) identified an 8-fold higher occurrence ($p<0.001$) of side effects amongst chronic non-cancer patients using opioids compared to controls [178]. The

average number of adverse events in the opioid-receiving group was 11.9, and the most frequently reported events were dry mouth (42%), sweating (34%), weight gain (29%) and memory deficits (24%).

In particular, tolerance to opioid-induced gastrointestinal disturbances does not usually happen, and the slowing effects of opioids on the bowel movements continuous to be a great risk during treatment [175]. Even though some immediate side-effects lessen and settle during long-term opioid use, some may not and can result in significant morbidity and a continued discontinuation of therapy [176, 179, 180]. Adverse events with long-term opioid use are increasingly being investigated and described in the literature, and the clinical implications are being acknowledged.

Recent literature has described respiratory depression as a concern and a risk in chronic opioid therapy. Webster LR et al. (2008) investigated the occurrence of sleep-disordered breathing in 140 chronic pain patients who were prescribed around-the-clock opioid therapy (short-acting opioids used 4 or more times a day within 24 hours, or used as long-acting preparations or both) for at least 6 months [181]. Patients underwent polysomnography overnight, which measured airflow, the frequency of apnoea (breathing cessation), hypopnoea (airflow reduction), heart rate and rhythm. Overall, 75% of patients were found to have experienced apnoea-hypopnea. Following the adjustments of demographic factors, both the addition of benzodiazepine (p=0.045) and an increase in morphine equivalent dose (p=0.002) were found to increase the severity of the experience. The daily dose of patients was found to be high, with median daily dosage of morphine equivalents of 187.5 mg/day (range 18.75–1,500 mg/day), which may possibly explain the link to apnoea-hypnoea.

Other respiratory disorders that have been noted to occur alongside long-term opioid use include reduced oxygen in the blood, and carbon dioxide retention [182, 183]. Respiratory depression has been shown to happen in a dose-dependent manner, and have been linked to mortality[184-186].

Opioids can also affect the endocrine system. Even though little research has investigated the influence of the drug class on the endocrine function, a study by Rhodin A et al. (2010) identified hypothalamic pituitary dysfunction in CNCP patients treated with strong opioids for over a year compared with a control group not treated with opioids [187]. The study described a reduction in hypothalamic-pituitary-growth-hormones amongst an opioid-treated group and symptoms that were directly linked to endocrine dysfunction, including decreased sexual function, reduced physical and emotional functions. These were found to be reversible with the reduction of opioid dosage or in ceasing opioid treatment.

Further to this, Deyo RA et al. (2013) demonstrated a greater prevalence of male patients with low back pain on long-term opioid therapy receiving erectile dysfunction or testosterone replacement therapy compared to those on short-term or no-opioid treatment [188]. The probability of receiving erectile dysfunction or testosterone replacement treatment also increased with increasing opioid dosage amongst long-term opioid users; a daily dose greater than 120mg morphine equivalent was found to be associated with more than 50% likelihood (OR: 1.58, 95%CI 1.03, 2.43) of being treated for erectile dysfunction.

Low bone mineral density is a common occurrence in musculoskeletal-related chronic pain conditions with links to risk of fractures. However, covariate analysis has also shown that opioids play a key role in fracture risk. A nested case-control study by Li L et al. (2013) selected

adult cases with first diagnosis of fracture of the hip, humerus, and wrists, from a large clinical database [189]. The study excluded crucial risk factors for fracture such as metabolic bone, Cushing syndrome, hyperparathyroidism, history of osteoporosis, alcohol and drug abuse.

Opioid exposure within a year of fracture was determined and the risk of fracture was compared between opioid users and non-users while controlling for important confounders, such as smoking, comorbidities (e.g. osteoarthritis, rheumatoid arthritis) and concomitant medication use (e.g. steroids). Risk of fracture was found to be significantly higher amongst current opioid prescription users in contrast with non-users; aOR: 1.27 (95%CI: 1.21, 1.33), and increased more than two-fold for every prescription used; aOR: 2.70 (95%CI: 2.34, 3.13). Likewise, in a different study, Saunders KW et al. (2010) reported a greater risk of fracture particularly in elderly patients (>65 years) with CNCP using opioids compared to the control group of non-opioid using CNCP patients, and the risk was twice (HR: 2.00, 95% CI: 1.24, 3.24) as high in patients using an average daily dose of ≥50 mg [190].

Prolonged opioid therapy or high doses have also been linked to cardiotoxicity and risk of irregular heart rhythms. Carman WJ et al. (2011) assessed the occurrence of myocardial infarction (MI) and coronary revascularization (CR) among a cohort of patients prescribed long-term high and low dose opioids, and compared the incidence to control groups not using opioids [191]. The study comprised of total of n=148,657 chronic opioid using patients and matched controls. Risk of MI was 2.7 times greater in patients using chronic opioids compared to control, with a 2.4 times greater risk of CR. Following the initial evaluation, the author added a third study group of patients prescribed long-term COX-2 selective NSAIDs (64,072 celecoxib users and 20,502 valdecoxib users) to compare the risk of MI with control. Long-term COX-2 users had 1.7-1.9 times higher risk of MI compared with control. The author thus

concluded that the risk of MI was greater in patients using chronic opioids relative to control and patients using chronic COX-2 NSAIDs.

Research on the harms associated with long-term opioid therapy has expanded over time and has included a description of aberrant drug-related behaviours with prolonged opioid use. Addiction is a neurobiological condition, which is affected by genetic, psychosocial and environmental elements [192, 193]. Addiction manifests itself as harmful, compulsive, persistent behaviour, with impaired control and cravings [193]. There has been a lack of well-controlled studies that have estimated the rate of addiction with long-term opioid therapy. Studies that have investigated addiction have concluded a potential risk of addiction amongst chronic non-cancer pain patients that do not necessary have a history of substance abuse, although the majority of patients who develop addiction tend to have a history of substance abuse [194-201].

Medicinal abuse is defined as the non-medical use of a substance or use of a medical substance other than what it was indicated for, often for recreational use [202]. Abuse of opioids during treatments can become an apprehension in medical practice and it has been suggested that examination of the prescribing patterns can be used as one of the main functions when evaluating the occurrence of treatment diversion [203]. In retrospective studies, patients with a history of substance abuse, and who were on long-term opioid therapy for chronic non-cancer pain, were also found to have depression, anxiety, and comorbidities [203, 204].

Equally, the risk of opioid prescription fatal and non-fatal overdose and deaths, which has increasingly been reported in the literature, has been shown to be associated with, but not limited to, the prescribed dose [185, 205, 206]. In a large cohort study by Liang and colleagues (2015) followed n=206,869 adult patients with non-cancer pain who were prescribed schedule II and III opioids greater than 3 months from their first opioid prescription use [207]. Patients'

demographic and clinical information were collected, and drug utilisation patterns were examined at 6-month intervals with a morphine equivalent daily dose computed accordingly. Following the adjustment of demographic and clinical morbidities and the use of psychoactive medications, the risk of opioid-related overdose was 2-fold higher with the use of 50-99mg (HR: 2.12, 95%CI: 1.7–2.63) and almost three times as high with the use of ≥100mg daily dose (HR: 2.56, 95%CI: 21.12–3.09).

Another issue with long-term opioid therapy is the phenomena of tolerance. This is a state in which repeated drug exposure can lead to changes that result in the diminished effect of the drug over time [208]. This can occur with the analgesic effects of opioids, and traditionally it was thought that increasing a drug dose would overcome its premises. However, on-going experience with long-term opioid therapy, coupled with recent evidence, shows that some patients report no further analgesic or contrariwise greater pain despite elevated high dose opioid use. It is yet not clear as to which facet of treatment, i.e. type of opioid drug, exact doses, or timing, triggers tolerance [209].

2.3.4 Summary of the evidence of long-term opioid use in chronic non-cancer pain

An overview of the literature on the utility of opioids in chronic non-cancer pain reveals good evidence for efficacy compared to placebo or non-opioid interventions in treatments that are for 90 days (12 weeks). However, results from randomized controlled trials suggest that a large number of patients are inclined to stop and withdraw from opioid use due to intolerable adverse effects or inadequate pain control. Nausea, vomiting, constipation and sedation are some of the more common adverse effects reported and the main reasons for trial discontinuations. Improvements in side effects with long-term treatments were not evident.

Although RCTs and open-label extension studies (>3 months/>12 weeks use) have been conducted, these have been limited, and many show little or no improvement in pain, function and quality of life, with indications that only a small subgroup of patients obtain pain relief, improved sleep and mood with long-term use. However, criteria that differentiate long-term opioid responders from non-responders, and the optimal therapeutic dose range that can be used for optimal outcomes, have not been identified and remain not clear enough to inform clinical practice. In addition, many trials (RCTs and open-label follow-up studies) exclude elderly patients and those with co-morbidities in fear of increased risk of predispositions to opioid-related harms. The trials were naturally conducted in controlled settings, often in specialised pain clinics, which further limits the generalizability of the evidence to non-specialised clinical practice settings.

Research beyond randomized trials that has also evaluated long-term opioid safety and effectiveness include observational studies and case reports. The results generated from the studies have been highly variable and subject to confounding. Nevertheless, some observational studies have indicated that pain reduction and improvements in function are not always met over long-term opioid use, and there are potential significant risks of harm to several organ systems that have not previously been known with short-term opioid use.

2.3.5 Commentary on quality of reviewed studies

Nine of the 16 reviewed RCTs assessed opioid outcomes for 12-weeks and were rated as high quality (score of ≥6) using the Cochrane Back Review Group Criteria, and had methodology designs that help to minimise coercions to internal validity. However, due to the short-term duration of the trials, the evidence generated (external validity) did not confirm the clinical usefulness and outcomes of opioids prescribed over long-term periods in CNCP. The remaining

RCTs (7/16) were open-label follow-ups of ≥12 weeks and scored low quality against the Cochrane Back Review Group Criteria. This was primarily due to a lack of treatment concealment, lack of patient and assessor blinding, lack of information on treatment compliance, insufficient information on co-interventions and high drop-out rate, leaving only a small sample of participants for outcome assessment (Appendix 4).

Although all the 17 systematic reviews reviewed were either rated as having minimal or minor flaws, they were of high quality according to Oxman and Guyatt's Criteria (Appendix 5). However, a majority of the reviews, which included both randomized controlled trials and non-randomized studies, were reported to be subject to significant bias due to: (a) heterogeneity in study design and study population; (b) small sample sizes (leading to few studies meeting inclusion criteria); (c) high rates of loss to follow-up; which, in turn, impacted on (d) inability to conduct pooled or meta-analysis; and (e) variations in internal and external validity of included studies.

As for observational studies, notably, the limiting factor in the quality was mainly the potential of selection bias, often due to the lack of a treatment comparator group. Furthermore, the susceptibility of confounding when estimating treatment effects further limited the conclusions on the treatment effects, despite the application of appropriate study designs such as matching, and statistical analysis such as adjusting for various variables, (Appendix 6).

2.3.5.1 Final conclusion on effectiveness of chronic opioid therapy

It can be concluded from the review that there is encouraging evidence of a preliminary (short-term) effectiveness of opioids for the management of chronic non-cancer pain. However, this does not foresee long-term efficacy and, currently, due to the limitations in the quality of

studies assessing long-term outcomes of opioids, the support of their prolonged use remains based on weak evidence. Hence, until higher quality evidence accumulates that also covers multiple important outcomes beyond pain and function, and that provides information on the circumvention of risks, the general use of opioids long-term in CNCP cannot be explicitly assumed.

2.3.6 Clinical guidelines for opioid therapy for chronic non-cancer pain

A number of international and national organisations, such as the American Society of Interventional Pain Physicians, the Canadian Pain Society, the Royal College of Anaesthetists Faculty of Pain Medicine, and the Australian and New Zealand Faculty of Pain Medicine, have generated practice guidance on the use of opioids in chronic non-cancer pain [47, 210, 211].

The guidelines are comparable in that they recommend the cautious use of opioids in carefully selected groups of patients who may not have responded well to other alternative analgesic treatments. They also advise on the assessment of patients for aberrant drug behaviours before treatment, the use of medication agreement contracts, regular monitoring, and the exercise of caution in the use of long-term opioid therapy. In addition, referrals to pain specialists are strongly recommended to patients who are at greater risk of opioid-related complications [47, 210, 211].

Recently, in 2016, NICE published an updated report on the pharmacological management of low back pain which advises on the avoidance of the routine prescribing of opioids for both acute and chronic low back pain [53]. The updated guidelines have also been expanded to encompass sciatica, due to the insufficient evidence of effectiveness of the medications in both conditions.

Meanwhile, NICE advises that in the clinical management of osteoarthritis, if paracetamol or topical NSAIDs provide inadequate pain relief, the addition of opioid analgesics could be considered [55]. However, from the time of the original NICE osteoarthritis recommendation (which was in 2008), a large Cochrane systematic review was conducted in 2014 which showed that opioids had a small and clinically questionable effect on pain and physical function, which was also contrasted by the risk of adverse effects [212]. Thus, it is yet to be observed if future guidelines will reflect and follow a similar line to the low back pain management guidance.

Evidence-based guidelines are known to serve as an important tool in clarifying best practice and play a key role in standardizing the level of patient care provided. Most of the developed guidelines on opioid therapy for chronic non-cancer pain have been established through professional consensus and the use of empirical clinical judgements, and validity has not yet been confirmed in clinical trials.

2.4 Patterns of opioid utilisation in chronic non-cancer pain

This section examines patterns of opioid utilisation in chronic non-cancer pain in the UK and aims to provide a contextual basis of the gaps in knowledge that the thesis sets to explore.

2.4.1 National utilisation

A number of studies in the UK have begun to examine the utilisation of opioids in primary care using different patient-level data sources. In 2015, Ruscitto A et al. (2015) conducted a geographically-defined study using patient-level population data of dispensed analgesics to examine the proportion of adults in Scotland who were dispensed opioids between 1995 and 2010 [213].

The study reported a decrease in users of weak opioids, but a significant increase in recipients of strong opioids, from 0.2% in 1995 to 3.6% in 2010. The rise was predominantly accounted for by the receipt of morphine, oxycodone, fentanyl and tramadol, suggesting a shift of prescribing from weak opioids to strong opioids. However, it was not clear whether the shift was related to the prescribing of opioids in cancer or non-cancer pain diagnosis, and there was no additional analysis of changes in dose or duration of opioid use, which makes it difficult to conclude about long-term opioid use in CNCP [213].

Similarly, in a different study by Bedson J et al. (2013), the prescribing of different types of analgesics in general practices in North Staffordshire was examined between 2002 and 2009 [214]. Trends of strong opioid prescription use were found to have doubled from 545 to 1035 patient users per 10,000 registered population. However, like Ruscittos' study, prescribing was examined irrespective of indication and hence it was unclear whether the trend was specific for patients with cancer or non-cancer related pain.

In a different study, Foy R et al. (2016) studied trends and factors affecting the prescribing of opioids in primary care [215]. The study used routinely collected medical records from general practices in Leeds and Bradford to determine patterns of opioid prescribing, including the stepping up or down of strong opioids. The author found an increase in the proportion of primary care patients prescribed at least one opioid from 6.6% to 12.8% over a period of 7 years, from 2005 to 2012, with an equivalent rise in patients using strong opioids from 0.13% to 0.85%. The likelihood for patients escalating treatment from weak opioids to strong opioids was highly variable between practices and was dependent on differential patient factors, such as: ethnicity, gender, age, number of "other" medications that the patients were prescribed, and the number of general practice consultations the patients had.

The study highlighted the various patient characteristics that may be associated with opioid prescribing in practice. However, the findings were a reflection of opioid prescribing in only two UK regions. Moreover, the analysis did not include an investigation of doses used, particularly amongst strong opioid users, which limited the ability to detect the relative risk of the prescribing practice, particularly in the stepping up of treatments to strong opioids [215].

Beyond the examination of opioid use in specific regions, a large cross-sectional study by Zin CS et al. (2014) used a national primary care database, the Clinical Practice Research Datalink (CPRD) to compare the utilisation of strong opioids in cancer and non-cancer pain patients from 2000-2010 [216]. The general patterns identified were that there was a substantial increase in both the number of cancer and non-cancer pain patients prescribed strong opioids, and in the number of prescriptions issued per patient.

The rise in prescribing in patients with non-cancer pain in the study was accompanied by an increase in the proportion of patients prescribed oral morphine equivalent daily dose >200mg/day. This could arguably indicate high-risk use; however due to the duration of the utilisation not being measured (e.g. as short-term or long-term opioid use) the high dose use could have inevitably been for short-term use purposes [216].

The increase in the prevalence of potent opioid use seen in the study by Zin CS et al. (2014) matched that of a study by Bedson J et al. (2016) who also analysed data on potent analgesics from CPRD [217]. However, the study only examined prescribing patterns of opioids in patients with musculoskeletal disorders over an 11-year period, from 2002-2013. Nevertheless, over one fifth (22.6%) of patients had been using the potent analgesics beyond 2 years, and the trend of length of use beyond 90 days per year also increased over time.

A different study by Chevalier P et al. (2014) set out to describe differences in opioid use patterns in non-cancer pain between UK and Germany, and also reported on long-term opioid use [218]. Approximately in 1 in 5 of the (UK) study populations, patients were prescribed opioids >183 days. The use was estimated as point prevalence and trend details of durations of drug use were not captured.

Two further studies followed primary care patients with musculoskeletal conditions over an extended period to evaluate strong opioid prescription use and identified factors influencing the utilisation. Green DJ et al. (2013) sent postal surveys to registrants aged >50 years with joint pain in practices in North Staffordshire [219]. Data on participants' demographics, health and psychological status, pain experience and analgesic prescription use were collected at baseline. It was estimated that nearly one fifth (19%) were prescribed opioids, and over one in

four (26.7%) who had severe joint pain at baseline were more likely to be recipients of opioids than those indicating mild pain. Duration and the dose of opioid therapy were undetermined, but it was indicative that physical function and pain intensity were important factors associated with the initiation of opioid therapy.

Within the same year, Ashworth J et al. (2013) published a study examining opioid use in low back pain and found significant differences in the characteristics of patients prescribed opioids [162]. Recipients of opioids had greater co-morbidities and pain intensity, and at 6-month follow-up there was no significant improvement in function. The research provided important evidence of outcomes with respect to opioid use in low back pain, but little evidence was provided on the prescribing patterns.

2.4.2 Unresolved issues and contribution of the thesis

Drug utilization research is often carried out in order to study the use of drugs in society, and is defined by the World Health Organization as '*the marketing, distribution, prescription and use of drugs, with special emphasis on resulting medical, social and economic consequences*' [220].

Such studies are able to answer questions related to how drugs are being used by making estimates of the amount and frequency of medication exposure at an individual level. This, in turn, enables the identification of prescribing activities and drug utilisation patterns that may be deemed inappropriate and that may predispose patients to disconcerting risks [221, 222].

The end purpose and focus of any drug utilization research is to improve the quality of medication use, where it is seen necessary, through the process of evaluating whether the

prescribing and distribution of drugs are rational and based on existing accurate and timely evidence. Drug utilization studies are also needed not only for the interest of regulatory control, but also for the basis of future healthcare planning initiatives and strategies as per the health needs of the examined population [221, 222].

While there is a pursuit of adequate pain management in CNCP, the prolonged utilisation of opioids is daunting as many uncertainties over their clinical use (weak evidence of efficacy and evidence of safety issues as described earlier) prevails, and their wide general use could pose potential public health implications [135, 150, 152, 223]. Furthermore, the national studies described earlier highlight that there remains a considerable gap in the knowledge of opioid/stronger opioid use in the UK, and several questions remain unanswered. This can be summed up to be related to limitations in the extent of long-term opioid utilisation nationally in non-cancer pain, identification of the relationships between patient factors and treatment, and the contextual involvement of healthcare resources use in prolonged opioid treatment.

As a result, further research in this field is required to update earlier epidemiological studies and allow room for new insights into the epidemiology of opioid/strong opioid use in the UK, in the hope of informing and fortifying appropriate evidence-based responses that could help manage and meet patients' health needs, while evading potential unwarranted drug-use related consequences. Thus, this thesis, which is a population-based research, sought to advance the understanding of (strong) opioid utilisation patterns in non-cancer pain patients in routine clinical primary care.

The thesis focused on the prescribing of four types of strong opioids that include: fentanyl, buprenorphine, oxycodone and morphine, which are defined in section 4.7.2 in the British

National Formulary [121]. This was done with the intention of evaluating potent opioids that are most likely to be used in chronic pain in primary care and that carry a greater propensity of risk due to their potency.

2.5 Research aims

The thesis aimed to examine characteristics, prescribing patterns, and the primary and secondary health care use of a nationally representative sample of primary care non-cancer pain patients prescribed strong opioids, with a particular interest in examining long-term utilisation.

2.6 Research questions

There were four overarching research questions that this thesis aimed to answer; which were categorised into four areas:

1) Utilisation trends:

a) What trend changes have occurred nationally between 2000-2010 in the utilisation (number of prescriptions) of strong opioids in primary care?

b) What is the prevalence and incidence of primary care non-cancer pain patients prescribed strong opioids between 2000 and 2010?

c) What is the prevalence and incidence of primary care non-cancer pain patients prescribed strong opioids long-term between 2000 and 2010?

2) Patient profiling:

a) What are the characteristics of non-cancer pain patients prescribed strong opioids in primary care?

b) What are the specific socio-demographic and clinical traits of recipients of long-term strong opioid therapy?

3) Treatment patterns:

a) What are the prescribing patterns in terms of number of prescriptions per patient, number of days of drug supply, and the daily dose use of strong opioid users?

b) To what extent does the prescribing pattern of long-term users differ from short-term users?

c) What are the factors influencing long-term strong opioid use in the sample studied in primary care?

4) Healthcare resource use:

a) What is the overall pattern of healthcare use (GP visits, referral to pain management specialist and in-patient admissions) of long-term users, and how has this changed between 2000 and 2010?

b) What are the causes of long-term users' hospital (in-patient) admissions, and what factors are correlated with long-term users' primary care and secondary healthcare use?

2.7 Rationale for the database and type of methodology used in the thesis

Data that were used in the thesis were extracted from a large primary care database known as the Clinical Practice Research Datalink. The database was chosen due to its extensive longitudinal clinical information, which is collected from a wide number of primary care practices (n=685) throughout the UK [224, 225]. This makes the database broadly representative of the UKs' primary care population.

The Hospital Episodic Statistics database, which is described in detail in a subsequent chapter (chapter 6, page 183), was also used, and linked with the initial data extracted from CPRD to analyse patients' hospital information. A combination of cross-sectional and longitudinal study

designs were adopted in the various chapters in order to appropriately meet the research questions.

A cross-sectional study design was chosen to examine a nationally representative cross-section of non-cancer pain patients in primary care prescribed strong opioids. This would allow for analysis of the prescriptions issued, and estimate the prevalence and incidence of prescriptions issued and the prevalence and incidence of patient users. The cross-sectional design was also ideal for describing traits of the users in terms of age, gender, type of non-cancer pain conditions diagnosed and comorbidities.

A longitudinal study design was adopted to examine treatment patterns and healthcare use of strong opioids users over time. In longitudinal studies, data variables for the same individuals are generally collected and repeatedly measured at multiple periods of time [(226)]. This makes the method appropriate for addressing research questions that deal with changes in drug exposure and outcomes of interest over time. Longitudinal data analysis is likely to produce time-varying and time-invariant variables, which can be examined in relation to a desired event. Moreover, longitudinal designs permit stronger inferences to be made about the direction of causality of the outcome and the longevity of its relationships to explanatory variables examined [(227)].

2.8 Data source

2.8.1 Introduction to the Clinical Practice Research Datalink

The CPRD is a longitudinal computerized primary care database, which is managed by the Department of Health, and jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare Product Regulatory Agency (MHRA). The database was initiated by a commercial company named VAMP Ltd in 1987. The company installed free computers in all general practices to facilitate the entry of patient clinical data, which could be used in post-marketing surveillance studies by the pharmaceutical industry [228].

In 1993, Reuters Health Information (an independent news agency disseminating information, including medical and research) acquired VAMP, and the database was donated to the UK Department of Health (DH) to be used for research on a non-profit basis. At the same time, the database was given the name of the General Practice Research Database by the DH, and has been managed by the MHRA since April 2003. Its name was subsequently changed to the Clinical Practice Research Datalink in late 2012 [228].

The CPRD contains anonymised records dating back to 1987 and up to the present, and holds approximately 13.7 million patients' records and 5.4 million active patients' records from 654 primary care practices across England, Scotland, Wales and Northern Ireland. This covers an estimated 8.5% of the UKs' population. Patients' data is collected from the Vision system, which is the standard system used by a majority of general practitioners, and is supplied by In Practice Systems Ltd (INPS) [224, 225].

2.8.1.1 Structure of the database

The data recorded and made available by the CPRD include patients' demography, clinical events, test results, prescriptions, referrals to specialists and medical history. There is also a series of additional data that are entered with more details about specific predefined events such as lifestyle indicators [229].

The data is organized and categorized into 10 separate files which include; patient, practice, staff, consultation, clinical, referral, test, therapy, immunization and additional file (Table 2-4). Each of the files contains a unique numerical patient identification code (except in the practice file, which contains numerical practice codes), which can be used to link information contained in different files. All patients in the database have their information recorded in each of the 10 files [229].

All clinical diagnosis and clinical events in the database are recorded using Read codes. This is a hierarchical clinical coding system of over 80,000 terms that are used in general practice in the UK [230]. Read terms cover signs, symptoms, diagnosis, investigations, treatment and administrative processes related to patients and their care. These are uploaded by the CPRD after necessary processing and quality checks are undertaken, and are added to the database for research use.

2.8.1.2 Quality of the database

All practices are required to record 95% of prescribing and patient-related events. Moreover, all data received by the CPRD goes through internal checks to ensure validation, continuity and completeness of the data. Practice level quality assessment is expressed as "up to-standard", and at patient level by a patient acceptability flag. The patient is indicated as either

acceptable or unacceptable to be used for research purposes once the entries have been checked [231]. Regular checks that are carried out by the CPRD include weekly numbers of consultations and prescriptions, completeness of prescribing, demographic, registration details, referrals, and patients' cause of death. Any data that does not meet the minimum standards are removed from the database [232].

Each practice is sent a validation report after each collection to inform them about the acceptability of the standards of the data, highlighting any discrepancies together with instructions of how to correct them [233]. A number of validation studies of the CPRD have been conducted over the years and have confirmed that the quality and completeness of the computer-recorded data is high [229, 231].

2.8.1.3 Ethical approval

Ethical approval for the use of patient information recorded in the General Practice Research Database needs to be sought and granted by the Independent Scientific Advisory Committee [234]. The use of the CPRD data in this thesis was approved by ISAC in 2013.

2.8.1.4 Features of CPRD for drug utilisation research

Many epidemiological studies investigating various diseases, drug use and healthcare service use have been conducted using data from the CPRD [235-239]. The population-based longitudinal nature of the database means that the data can be used to determine incidence and prevalence of events of interest over time. The database has also been used in pharmacoeconomic studies in order to assess resources used and costs associated with the management of a particular disease [240, 241].

2.8.2 Strengths of using CPRD in health research

The main advantage of using the CPRD database is the comprehensiveness of patients' medical records, which are derived from the UK primary care population cross-regionally. Thus, CPRD provides information that is representative and generalizable to the general primary care population. In addition, CPRD contains longitudinal data, which makes it feasible and ideal to study trends in prescribing, medial use and health service use long-term, thus meeting the research requirements of this thesis. The database has a track record for contributing to research involved in disease conditions, drug utilisation, drug safety, etc. [237, 242-244]

The participation of a large number of practices in CPRD allows researchers to efficiently study patterns of disease conditions and drug use nationally or in specific regions [224]. An important feature of the CPRD is its linkage to other healthcare databases (e.g. linkage to Hospital Episode Statistics), disease registers and death certificates, which allows for the study of continuity of care in different healthcare settings [229].

2.8.3 Limitations of using CPRD

The use of CPRD is an extremely prevailing and powerful tool for investigating primary care medical records. However, the completeness and quality of data depends on the computerized entries of information from registered practices [229]. In addition, a number of lifestyle variables, such as smoking, weight, height, are available for 70% of the population in the database, whereas socio-economic status information is not recorded at all [228]. This would need to be obtained through a third party: the NHS Digital (Index of Multiple Deprivation and Townsend Scores deprivation data). Furthermore, some of the linked information (such as HES data) is only available for practices registered within England, causing missing data of other countries within the UK [229].

Table 2-4 Divisions of files in the Clinical Practice Research Datalink

CPRD data files	Information
Patient	Patient demographics and registration details (e.g. registration date, transfer-out date, reason for transfer)
Practice	Details of regions of each practice and collection information
Staff	Records of role and gender of practicing staff entering the data
Consultation	Type of patient consultation (e.g. night visit emergency, surgery), date and duration
Clinical	Records on patient diagnostic diseases, their signs and symptoms, and severity
Additional clinical details	Additional patient information such as lifestyle and preventative risk factors (e.g. smoking, alcohol, exercise, diet and body mass index)
Referral	Details on patient referrals to external care (such as hospital inpatient or outpatients, specialist clinics), sources of referrals and types of referrals (first visits or follow ups)
Immunization	Details of type, method and stage of immunization.
Test	Results of biological tests.
Therapy	Details of medical prescriptions.

Note: adapted from Herrett E et al. (2015) [229].

Chapter 3 Trends in the prevalence and incidence of non-cancer pain patients prescribed strong opioids in primary care

3.1 Introduction

The prevalence of strong opioid prescribing in primary care has only been estimated in two previous studies. One study used regional primary care data from 12 practices in North Staffordshire to investigate trends in opioid prescribing in the region from 2002 to 2009 [214]. The author calculated the yearly number of adult patients prescribed potent opioids per 10,000-registered population as the primary outcome measure. The prevalence of strong opioid prescribing was found to have doubled during the 10 years from 507 to 1032 per 10,000-registered population. The rise was particularly noticeable with the prescribing of morphine and oxycodone, which collectively increased from 38 per 10,000 to 74 per 10,000.

The second study used a large national primary care database, the Clinical Practice Research Datalink (CPRD), to estimate changes in the prescribing of four strong opioids (buprenorphine, fentanyl, oxycodone and morphine) from 2000 to 2010 [216]. In the same manner as the previous study, the prevalence of strong opioid prescribing was calculated by repeatedly measuring the yearly number of patients prescribed the potent opioids per thousand patients that were registered in CPRD. The study reported a substantial rise in the prescribing of strong opioids by 466.2%, from 1.8 to 9.2 per 1000 registered patients.

However, none of the studies have assessed primary care prescribing of strong opioids long-term, which is defined in the literature as a supply of greater than 90 days [137]. Moreover, although one recent study published in 2016 examined long-term opioid prescribing using primary care data from CPRD, it assessed opioid prescribing in patients with musculoskeletal conditions only [217]. Thus, limited information remains on the prescribing to wider groups of non-cancer pain patients, and the extent to which the prescribing is for short-term or long-term

use, or both remains to be determined. Assessing changes in strong opioid prescribing over time with respect to prescription duration would be an important first step in quantifying the scope of the use of the potent drugs at a national level, and would be of value as a population-level surveillance method. The findings would also provide the background context and direction of the investigations in subsequent chapters.

3.2 Aims and objectives

The aim of this study was thus to analyse changes in the prevalence and incidence of strong opioid prescribing in non-cancer pain patients in primary care, from 2000 to 2010.

The specific objectives of the chapter were to:

1. Evaluate the overall trend in number of strong opioid prescriptions issued between 2000-2010 nationally (in the four UK countries).
2. Estimate the annual incidence and prevalence of non-cancer pain patients prescribed strong opioid per 10,000 person-years over the 11 years.
3. Estimate the incidence and prevalence of strong opioid users per 10,000 person-years according to durations of drug supply.

3.3 Methods

3.3.1 Study design

This study used a cross-sectional study design with linear trend analysis to examine annual prescribing of four strong opioids: fentanyl, buprenorphine, oxycodone and morphine, using the UK database CPRD from 1st January 2000 to 31st December 2010.

3.3.2 Study subjects

All pharmaceutical drugs, medical appliances and devices exist in CPRD as multiplex codes known as product codes. The CPRD provides an inbuilt product dictionary in which medical products of interest can be searched and the corresponding product codes identified. The identification of product codes is achieved by specifying either the drug substance name or the British National Formulary (BNF) code of the chapter and section of the drug of interest in the dictionary (Appendix 1).

Prescriptions of the four strong opioids were identified in CPRDs' inbuilt product dictionary by specifying drug names of each of the strong opioids e.g. oxycodone, morphine, etc. This generated a list of product codes, which included both the generic and brand names of each of the drug-classes (Appendix 7). The research team, which included a clinical expert, reviewed the list to ensure its inclusiveness, and a consensus was reached to exclude product codes corresponding to injection and suppository formulations as these are often less likely to be prescribed in primary care. Moreover, product codes for buprenorphine sublingual 2mg and 8mg were also excluded due to their common indication for opioid misuse and dependence treatment [121].

The list of product codes generated was subsequently applied to patients' therapy file to identify and included adult patient (>18 years at time of first prescription use; recorded on or after 1st of January 2000) who had one or more of the strong opioid prescriptions issued between 2000-2010. Each prescription had to have been within the up-to-research standard date (which is the date before the practice was deemed to be of good quality for research according to CPRDs' quality control criteria) and within patients practice registration start and end date.

The prescription data was further combined with patients' clinical, referral and consultation files to determine patient's medical diagnosis, and subsequently enable the exclusion of patients with cancer diagnosis. All diagnostic events in CPRD are identified through Read codes. This is a coded thesaurus system of medical terms that are commonly used in UK general practice and was developed to standardise the recordings of clinical information throughout the NHS[231].

Read codes are organised in a hierarchical structure and into five alphanumeric codes, using numerical 0-9 and letters A-Z to accurately describe clinical events, with the specificity of the clinical description increasing down the hierarchy [230]. This means that the Read codes become more disease and site specific further down in the hierarchical structure [245]. For example, for the Read code B136; the first level represents the diagnostic chapter, i.e. B= neoplasm; the second level, B1 specifies that the neoplasm is malignant; the third level, B13 indicates the site of the neoplasm, which is stomach carcinoma; and the fourth level, B136 defines the character of the lesion e.g. carcinoma greater curvature stomach.

CPRD provides a medical browser in which Read/OXMIS codes for diagnostic conditions can be determined through the application of search terms [229]. The browser was used to ascertain Read codes related to cancer diagnosis by applying search terms such as cancer, malignant, neoplasm, tumour, carcinoma, etc. The comprehensive list of Read codes generated was reviewed and the final list was agreed by a consensus decision-making process and used in a previous publication by Zin CS et al. (2014) [216] (Appendix 8).

In addition to Zin CS et al.'s (2014) cancer Read codes, the list was further supplemented with the quality and outcomes framework (QOF) cancer codes, version 27 to further ensure the comprehensiveness of the codes [246]. The quality and outcomes framework is a financial incentive scheme, which was initiated as part of the new General Medical Services (GMS) contract in April 2004 [246]. The scheme remunerates general practices for their performance against a range of quality indicators formulated by the GMS to improve the care and services for a number of defined chronic diseases. The QOF was designed to monitor long-term conditions, including cancer, and help in funding further improvements in clinical care. The QOF business rules specify Read codes for each included condition, and several studies have verified the validity of using QOF Read codes in CPRD data [229, 231, 247].

The list of Read codes was applied to the CPRD dataset and patients with cancer code(s) recorded 12 months within their first strong opioid prescription date were defined as cancer patients and excluded. The remaining patients were defined as non-cancer users. Recorded clinical events prior to the up-to-standard practice date were not included due to poor data quality.

3.3.3 Data management

The prescription data consist of information such as strength, quantity and dose. Prescription dose in CPRD is recorded as numerical entries, which are derived from an algorithm developed by CPRD to extract a numerical daily dose (NDD) from the dosage text instructions.

3.3.3.1 Data cleaning and managing missing data

The prescription data underwent a series of data checking and data cleaning procedures to amend any discrepancies prior to analysis. This process ensured:

- Valid gender and birth-year
- Maximum age was ≤107 years at last collection date
- First practice registration date was on or after birth date
- Current practice registration date (crd) was valid and on or after birth date and was on or after first registration date
- Practice transfer out of date (tod) was on or after first registration date and on or after current registration date (crd)
- Up to research standard date was on or before the index date

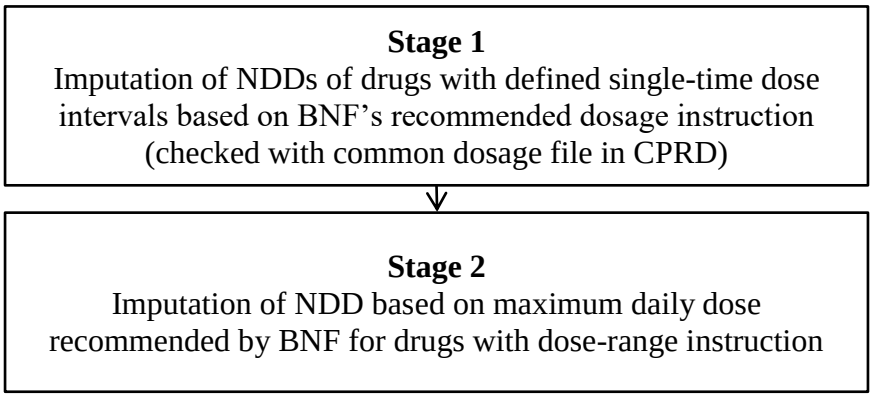
Further to this, all the extracted prescription data were checked for missing data. It was found that 34.48% of the prescriptions in the dataset (n=768,376) had missing numerical daily dose (NDD) values. The missing dose was managed into two stages (Figure 3-1) and in both stages, the British National Formulary (BNF) was used as the most appropriate guidance for dose recommendations and for imputation [121].

In the first stage, prescriptions with missing numerical daily dose of strong opioids that are recommended for use at defined single time-intervals were imputed on the basis of the daily

dose information provided by the BNF. For example, the BNF recommendations for fentanyl 25mcg/hour patch is 1 patch to be used every 72 hours; thus, the daily numerical dose or NDD for fentanyl 25mcg patch would be 0.33, and this was imputed as such [121].

However, not all opioid drugs are known to have definitive single time dose instructions. Doses may be recommended as a range of dosing-frequency to allow for varied pain intensities and thresholds to be controlled. For instance, according to the BNF, OxyNorm (oxycodone) 5mg capsules have a dose recommendation of one to be taken every 4-6 hours, or in the case of Temgesic (buprenorphine) sublingual tablets 0.2mg, one to be taken every 6-8 hours [121]. In such cases and in stage 2 of the imputation strategy, the BNF's recommended maximum daily dose of the drug was used for imputation, and this was based on the assumption that the maximum daily dose would be prescribed. For example, oxycodone capsule 10mg is recommended by the BNF as one capsule to be taken every 4-6 hours, thus the maximum daily dose which was every 4 hours was used as the information for imputation, hence the NDD imputed corresponded to 6 (maximum 6 tablets daily) (Figure 3-1).

Figure 3-1 Strategy for imputing missing NDD



3.3.3.1.1 Imputation diagnostic

Summary statistics such as mean, median, standard deviation and interquartile ranges were used to compare the distribution of the NDD data both before and after the imputation for data consistency. Before imputation, the midpoint frequency distribution of the data was 2 (IQR: 0.33, 3) (Table 3-2). The first step of the imputation process resulted in 87.15% of NDD values imputed, and the second step completely imputed the remaining missing NDD values (12.85%) (Table 3-1). The imputed data resulted in almost no change in midpoint frequency distribution of NDD, indicating consistency in the final imputed dataset, which remained a non-normal, positively skewed NDD data distribution.

Table 3-1 Results of NDD imputation

		Stage 1	**Stage 2**
Drug	**No of prescriptions with missing NDD (%)**	**No of NDD-prescriptions imputed (%)**	**No of NDD-prescriptions imputed (%)**
Fentanyl	171,623 (22.34)	163,927 (95.52)	7,696 (4.48)
Buprenorphine	135,517 (17.64)	101,514 (74.91)	34,003 (25.09)
Oxycodone	87,296 (11.36)	30,318 (34.73)	56,978 (65.27)
Morphine	373,940 (48.67)	373,912 (99.99)	28 (0.0075)
All	768,376	669,671 (87.15)	98,705 (12.85)

Table 3-2 Results of NDD imputation- diagnostic

NDD data					
Observed data (without imputation)			**Imputed data (stage 1 & stage 2)**		
Mean (SD)	Median	IQR (IQR range)	Mean (SD)	Median	IQR (IQR range)
3.28 (6.94)	2	2.67 (0.33-3.00)	3.34 (6.01)	2	3.67 (0.33-4.00)

Several other approaches for imputing the missing prescription numerical daily dose data prior to deciding on the final approach adopted were considered. The methods included:

1) **Hot deck imputation**: this approach uses known NDD of prescriptions issued for the same drug prescribed to the same patient [248]. The issue with this method is that it assumes that patients in the dataset have had the drug before, which is not always the case, and hence the approach would not be useful for prescriptions with missing NDDs that were only prescribed once.

2) **Mean/Median imputation**: this approach is a population-based imputation method in which the mean or median of NDDs of the same drug is prescribed to a group of patients with similar demographic traits e.g. age, gender etc. This method preserves the sample size; however, the variability and standard deviation of the data is reduced and there is an underestimation of variance [248].

3) **Multiple imputations**: the technique replaces each missing NDD measure with values that signify the conditional distribution of the observed variables in the data. This creates a set of multiple data, which is examined, combined and used for imputation [249]. The multifaceted approach was not considered to be a justifiable way of imputing the missing NDDS since doses could be predicted from reliable available resources and guidelines such as the BNF.

3.3.3.2 Prescription days' supply

The total number of prescription days' supply of strong opioids per year was calculated for each strong opioid user in the dataset. This was derived by dividing prescription drug quantity

by the numerical daily dose (NDD) of the drug, and the overlapping days of supply between prescriptions within the years were subtracted.

$$\text{Number of days' supply} = \frac{\text{Quantity prescribed}}{\text{Numerical daily dose (NDD)}}$$

Patients from the overall sample population who received a long-term drug supply in any one-year during the 11 years of the study were established, and long-term use was defined as individuals who had a total days' supply of greater than 90 days/year. This definition has been previously been used to define long-term opioid use in the literature [137].

3.3.4 Study outcome measures

3.3.4.1 Number of prescriptions

The total number of strong opioid prescriptions were repeatedly measured yearly from January 2000 to December 2010 and used as one of the study outcomes. The annual prescription data were further stratified according to the UK country data, which included England, Northern Ireland, Scotland, and Wales, to assess changes in prescription quantities nationally.

3.3.4.2 Prevalence of strong opioid users

The annual prevalence of strong opioid users between 2000-2010 was determined by dividing the total number of patients registered in CPRD who were prescribed at least one strong opioid prescription during the year of investigation (numerator) by the total number of age-eligible (≥18 years) patient-years in the same year (denominator). Patient-years was defined as the sum of the number of years contributed by each patient in CPRD at risk of being prescribed a strong opioid during the study period.

Patients who had a strong opioid prescribed in more than a year during the 11-year study period were included in the overall prevalence of use computation in each of the year that the drug(s) were prescribed (hence included multiple times over the study period, accordingly).

Prevalence in person-years of patients prescribed strong opioids by duration of drug supply and by drug formulation was also determined. Long-acting formulations were defined according to product information as opioids, which released drugs gradually into the bloodstream and needed to be taken less frequently than every 6-8 hours. Examples include: MST continus (LA morphine), OxyContin (LA oxycodone), Durogesic DTrans (LA fentanyl) [250]. Short-acting strong opioid formulations produce a quick increase and decrease in serum levels when administered, and produce an analgesic effect within 30 minutes. Examples include: Sevredol (SA morphine), Actiq (SA fentanyl), OxyNorm (SA oxycodone) [250].

3.3.4.3 Incidence of strong opioid users

Annual incidence of strong opioid users was also determined for each year from 2000 to 2010. Incidence cases were defined as patients who did not have a strong opioids prescribed in the previous year, but thereafter. This was calculated by dividing the number of new strong opioid users (numerator) in the calendar year by the total patient-years of age-eligible (≥18 years) patients registered in CPRD in the same year (denominator). New users had to have had their first prescription recorded after the start of the 'up-to-standard date'. The annual incidence was estimated from 2001 and onwards. This was because the study began in 2000 (data entry), and data prior to 2000 was of no avail to confirm incidence rates in 2000.

3.4 Data analysis

3.4.1 Descriptive analysis

The annual number of prescriptions of each of the four strong opioids was reported as frequency and percentage, and was plotted over the study period to provide a visual description of the utilisation. Although denominator population, which was the adult population registered in CPRD, increased by 40% from 2000 to 2010, however, the population continued to remain considerably stable from 2006 onwards. It was thus reasonable to examine and present annual trends of strong opioid utilisation in total number of prescriptions over time (Appendix 9).

The prevalence and incidence rates of strong opioid users were reported per 10,000 person-years (with a 95% confidence interval). Furthermore, the age/sex distribution of the denominator population was largely stable over the 11-years, and hence it was not considered necessary to standardize the annual prevalence and incidence measures for the age and sex distribution to the population of England; thus, un-standardised figures were reported (Appendix 9).

The total days' supply was stratified and analysed into four categories: 1-30 days, 31-90 days, 91-120 days and >120 days.

3.4.2 Trend analysis-annual percent change (APC)

Trends in prescriptions, prevalence and incidence of strong opioid users over time were measured by calculating the annual percent change (APC). This measure quantifies the magnitude of increase or decrease in the estimated rates per year in the time trend and essentially tests the null hypothesis that the APC is different from 0% [251, 252].

The annual percent change was calculated by fitting a linear regression to the natural logarithm of the annual number of prescriptions, incidence or prevalence rates using year as the independent variable, and the outcome measures as the dependent variable under the assumption of constant rate change over fixed intervals. The annual percent change can only be derived from linear regression model in a log scale, hence it was essential to log transform the outcomes measures of the study [252].

In addition to estimating APC for the overall trend of each of the outcome measures from 2000-2010, notable time-points in which the trend significantly changed and the magnitude of change over the 11 years were also detected using joinpoint regression model. This was computed by fitting joined log-linear segments, which joins different line segments together on a log-scale, and the intervals of significant changes are characterized by an APC [252].

In fitting the model, the number of joinpoints to be tested had to be specified; according to the graphical plots of the prevalence and incidence rates of strong opioid prescribing over the 11 years, it was apparent that there was a maximum of two joinpoints for the data, thus a minimum of 0 and a maximum of 1 was allowed for the analysis. The location of the joinpoints was determined using the gridsearch method, which was the default setting (and the sole option) in the joinpoint regression program [252]. Gridsearch method functions by generating multiple networks or grids of likely placements of joinpoints guided by the parametric settings (Appendix 10), and measures the sum square of errors (SEE) at each placement and detects the best fit.

The statistical significance of joinpoints was tested using Monte Carlo simulation based on a permutation test [251]. This method makes no assumption of distribution of the data and yields

a more accurate p-value by initially calculating multiple test statistics by randomly permuting the data several times and finally comparing the original test-statistic value with the permutated distribution of test statistics. The default number of permutation used was 4499, as suggested in the joinpoint statistical software (Appendix 10).

The analyses were conducted using STATA, version 14.0 (Stata Corporation, College Station, TX, USA) and Joinpoint Regression Program, version 4.5.0.1 Statistical significance was set at $p < 0.05$.

3.5 Results

3.5.1 Trends in strong opioid prescriptions

A total of 2,228,266 prescriptions of fentanyl, buprenorphine, oxycodone and morphine were issued between 2000 and 2010. Overall, morphine was the most frequently prescribed strong opioid with 1,040,263 (46.68%) prescriptions, followed by buprenorphine with 430,426 (19.32%), fentanyl with 414,663 (18.61%) and oxycodone with 342,914 (15.39%) prescriptions.

The number of prescriptions issued increased steadily over the 11 years by an annual percent change of 27.23% (95%CI: 24.90, 29.60) from 41,143 in 2000 to 443,312 prescriptions in 2010. Moroever, the number of prescriptions increased at a higher rate than the denominator population, and during the stable period for the denominator population from 2006 onwards, there was still a continuous increase in the prescription count. Analysis of the data within the four UK countries showed that the overall proportions of prescriptions rose annually by 25.75% (95%CI: 23.70, 27.90) in England, 36.23% (95%CI: 32.80, 39.80) in Northern Ireland, 32.40% (95%CI: 27.60, 37.40) in Scotland and 31.37% (95%CI: 28.30, 34.50) in Wales (Figure 3-2, Figure 3-3, Figure 3-4, Figure 3-5).

The highest number of prescriptions issued in each year was with morphine in England, Wales and Scotland, and buprenorphine in Northern Ireland (Table 3-3). However, the greatest change in the count of prescriptions per year was with oxycodone. The annual percent change in oxycodone prescriptions issued was 51.51% (95% CI: 37.00, 67.50, $p<0.001$) in England, 57.42% (95% CI: 39.50, 77.70, $p<0.001$) in Scotland and 55.06% (95% CI: 37.40, 75.00, $p<0.001$) in Wales, whereas in Northern Ireland, changes in buprenorphine prescription rose by 56.63% annually (95% CI: 49.90, 63.70, $p<0.001$).

Figure 3-2 England: Annual number of prescriptions of the four strong opioids, 2000-2010

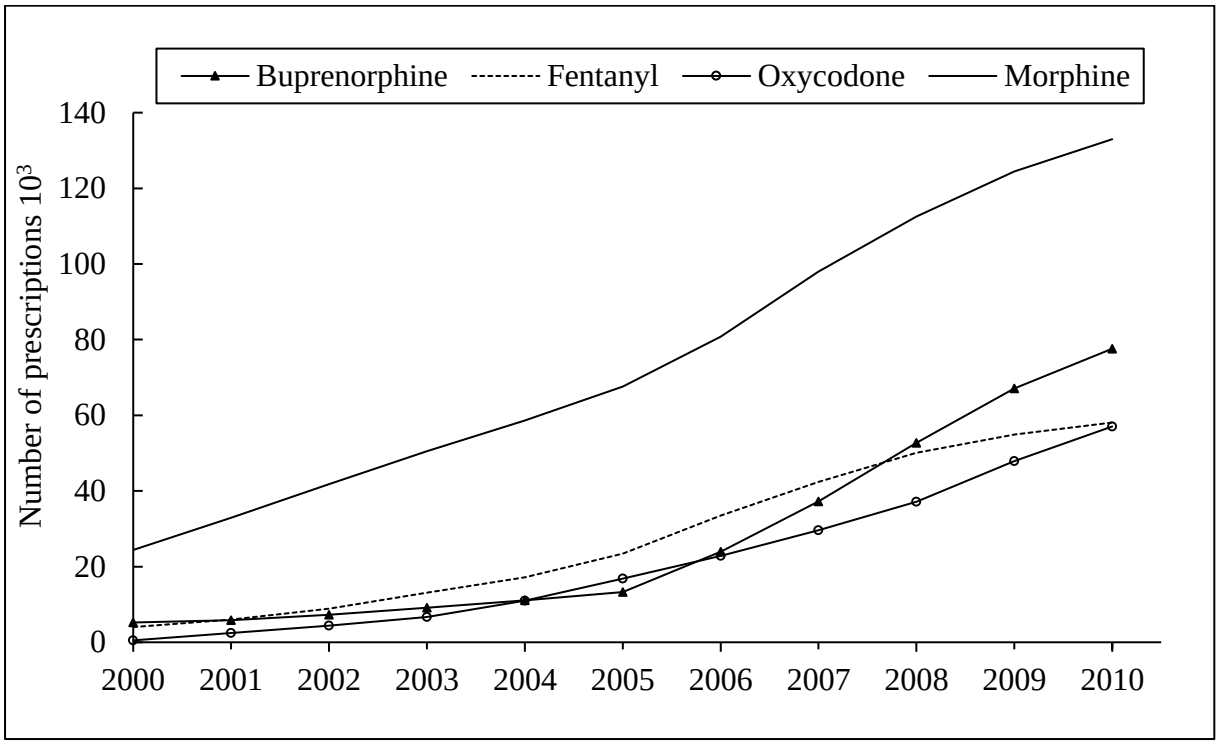


Figure 3-3 Northern Ireland: Annual number of prescriptions of the four strong opioids, 2000-2010

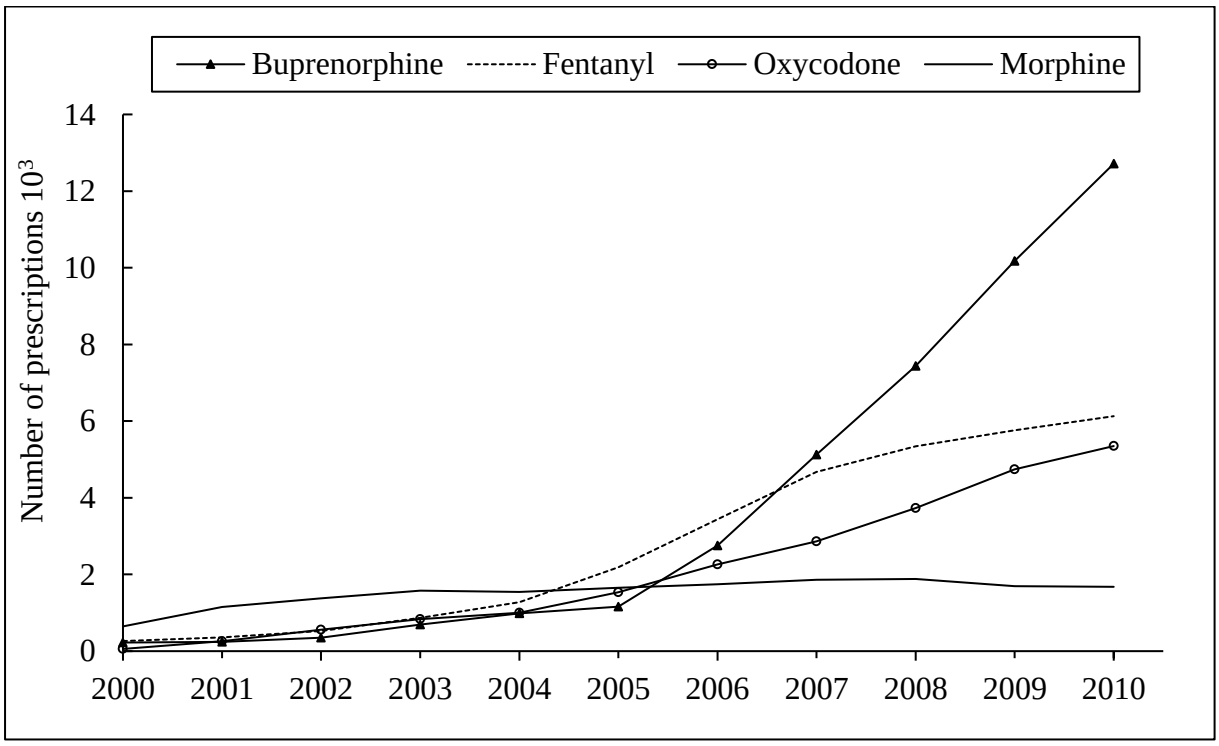


Figure 3-4 Scotland: Annual number of prescriptions of the four strong opioids, 2000-2010

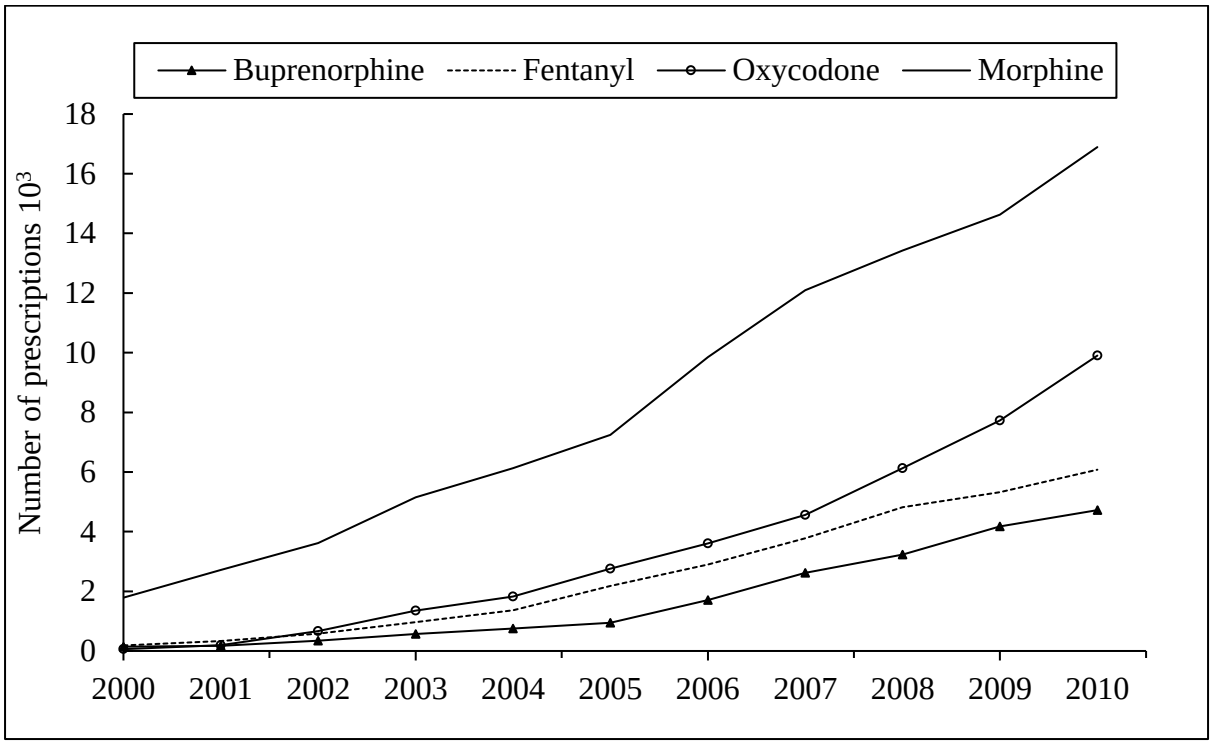


Figure 3-5 Wales: Annual number of prescriptions of the four strong opioids, 2000-2010

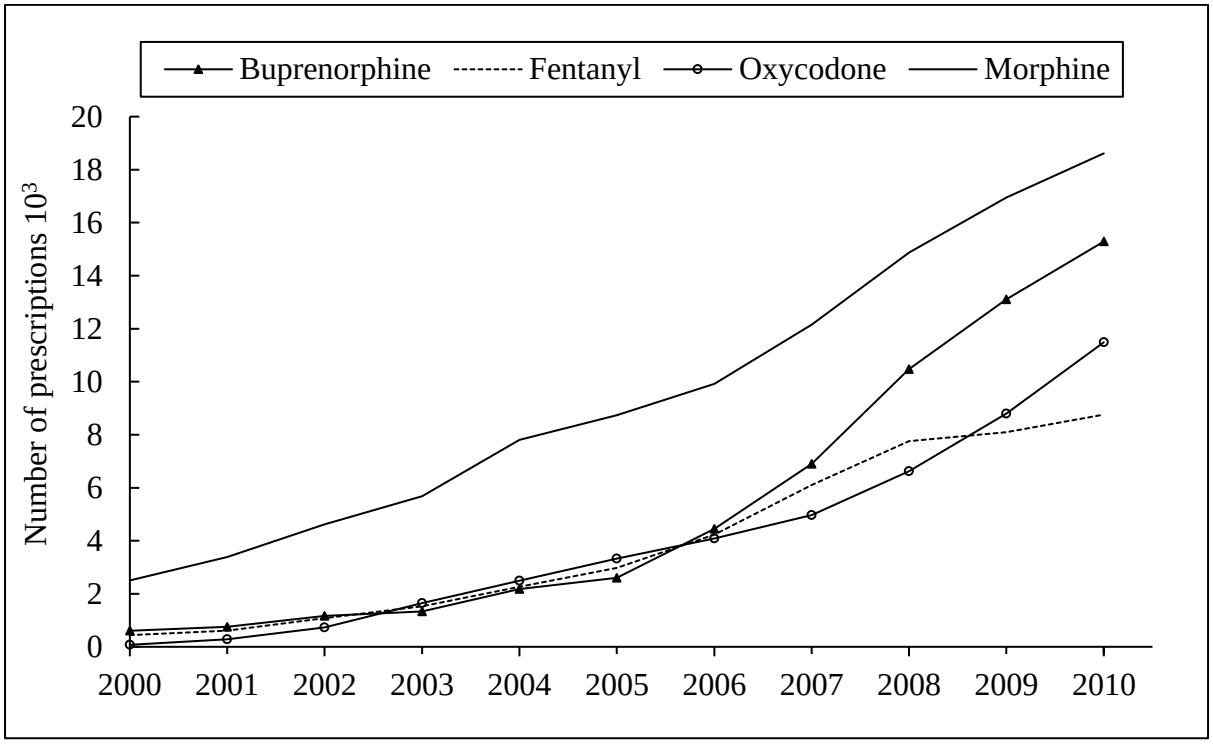


Table 3-3 Annual percent change (APC) of strong opioids prescriptions by drug in the four UK countries

Region	Number of prescriptions	Prescriptions in 2000	Prescriptions in 2010	APC (95%CI)
England				
Fentanyl	311,489	4,018	58,086	31.85 (26.50-37.40)*
Buprenorphine	310,319	5,229	77,597	34.72 (29.80-39.80)*
Oxycodone	236,400	500	57,042	51.51 (37.00-67.50)*
Morphine	824,701	24,402	132,980	18.22 (16.10-20.30)*
Total	1,682,909	34,149	325,705	25.75 (23.70-27.90)*
Northern Ireland				
Fentanyl	30,828	263	6,129	41.51 (33.80-49.70)*
Buprenorphine	41,863	225	12,714	56.63 (49.90-63.70)*
Oxycodone	23,206	58	5,350	48.06 (34.00-63.60)*
Morphine	16,804	646	1,676	7.27 (2.50-12.30)*
Total	112,701	1,192	25,869	36.23 (32.80-39.80)*
Scotland				
Fentanyl	28,511	185	6,077	41.78 (33.70-50.30)*
Buprenorphine	19,391	144	4,721	44.81 (39.30-50.50)*
Oxycodone	38,791	61	9,902	57.42 (39.50-77.70)*
Morphine	93,525	1,788	16,891	24.48 (20.60-28.50)*
Total	180,218	2,178	37,591	32.40 (27.60-37.40)*
Wales				
Fentanyl	43,835	440	8,759	36.98 (31.00-43.20)*
Buprenorphine	58,853	605	15,287	41.46 (37.80-45.20)*
Oxycodone	44,517	75	11,487	55.06 (37.40-75.00)*
Morphine	105,233	2,504	18,614	21.84 (19.10-24.70)*
Total	252,438	3,624	54,147	31.37 (28.30-34.50)*

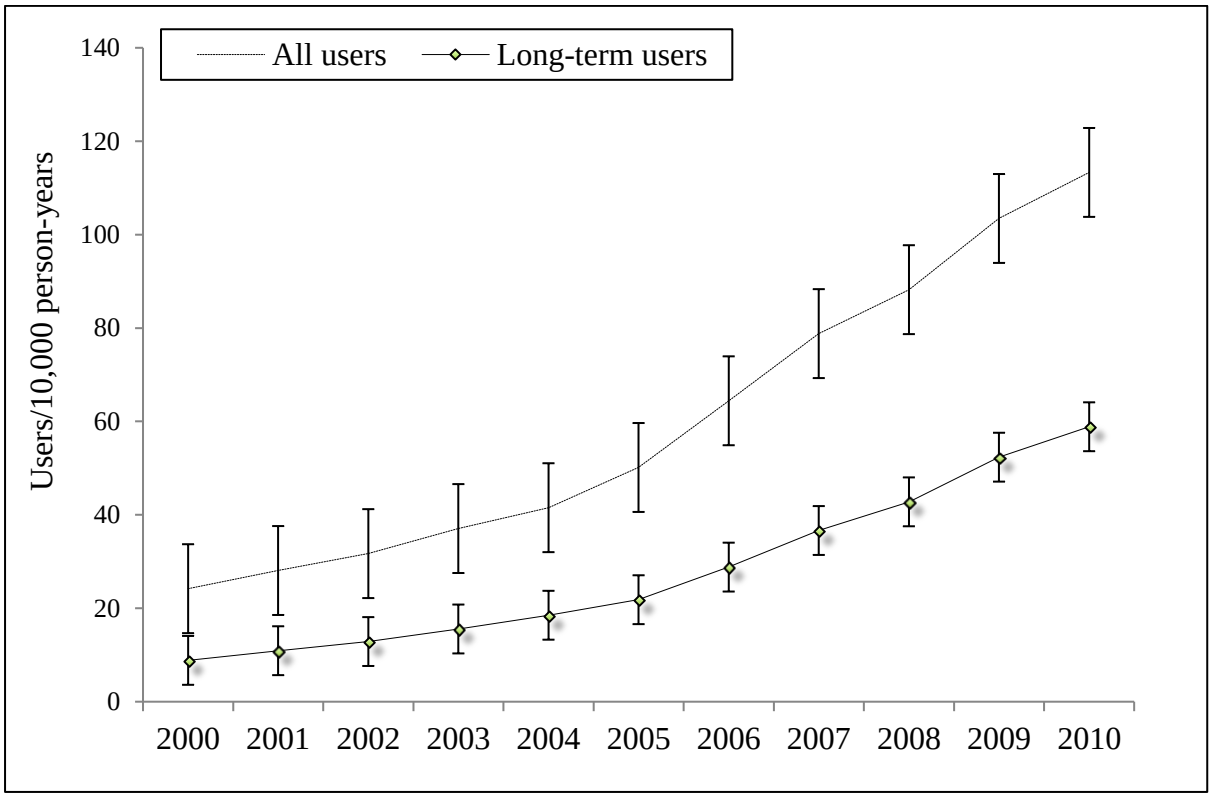
*Annual percent change (APC) is statistically significant ($p \leq 0.05$) different from 0.

3.5.2 Prevalence of strong opioid prescription users

Strong opioid prescriptions were issued to an estimated 135,941 non-cancer pain patients in CPRD between 2000-2010. This represented a point prevalence of strong opioid users of 32.85 (95%CI; 32.68, 33.03) per 10,000 person-years.

The overall prevalence of non-cancer pain patients prescribed strong opioids continued to initially grow steadily by 15.28% (95%CI: 13.90, 16.70, p<0.001) per year from 24.19 (95% CI; 23.62, 24.76) per 10,000 person-years in 2000 to 50.14 (95%CI; 49.44, 50.85) per 10,000 person-years in 2005 (Figure 3-6). This was followed by a rapid increase by 17.39% (95% CI: 13.10, 21.80, p<0.001) per year beyond 2005, up until the end of the study in 2010 (113.31 per 10,000 person-years).

Figure 3-6 Annual prevalence of strong opioid users, 2000-2010.



3.5.3 Prevalence of strong opioid users according to days' supply

The prevalence of long-term strong opioid prescribing (>90 days) also increased markedly in each year during the study period (Figure 3-6). In 2000, 8.84 (95%CI: 8.50, 9.19) per 10,000 person-years were prescribed a total supply of >90 days. By 2010, this had risen to 58.87 (95%CI: 58.12, 59.61) per 10,000 person-years, representing an APC of 21.59% (95%CI: 20.60, 22.60, p<0.001). Changing trends in prescribing were also observed according to the four categories of the total number of days (1-30 days, 31-90 days, 91-120 days, >120 days) of strong opioid supplied per year. Data indicated that in 2000, more prevalent users had an overall strong opioid supply of less than 30 days; 9.91 (95%CI: 9.55, 10.28) per 10,000 per person-years. However, over time, more users received >30 days' of strong opioids per year (Table 3-4).

In particular, the prevalence of users with >120 days' supply increased at the highest annual rate of 22.19% (95%CI: 21.20, 23.20, p<0.001) from 7.54 (95%CI: 7.22, 7.86) per 10,000 person-years in 2000 to 52.71 (95%CI: 52.01, 53.41) per 10,000 person-years in 2010. This was followed by users receiving between 91-120 days, which rose by an annual percentage rate of 17.60% (95%CI: 16.00, 19.20, p<0.001). The trend in days' supply was reflected in the overall average days' supply per user per year, which was 132.42±125.56 days.

Table 3-4 Prevalence of strong opioid users according to total days' supply/year

	Prevalence/10,000 person-years (95%CI)			
Year	**1-30 days**	**31-90 days**	**91-120 days**	**>120 days**
2000	9.91 (9.55-10.28)	5.44 (5.17-5.71)	1.30 (1.17-1.43)	7.54 (7.22-7.86)
2001	11.17 (10.80-11.54)	5.99 (5.72-6.27)	1.63 (1.49-1.78)	9.28 (8.95-9.62)
2002	11.83 (11.47-12.19)	7.00 (6.72-7.28)	1.77 (1.63-1.91)	11.11 (10.76-11.46)
2003	13.66 (13.28-14.04)	7.85 (7.56-8.13)	2.15 (2.00-2.30)	13.41 (13.04-13.79)
2004	14.39 (14.01-14.77)	8.64 (8.34-8.93)	2.33 (2.18-2.48)	16.18 (15.77-16.58)
2005	17.68 (17.26-18.09)	10.63 (10.31-10.95)	2.67 (2.51-2.84)	19.16 (18.73-19.59)
2006	21.50 (21.04-21.95)	14.11 (13.74-14.48)	3.53 (3.35-3.72)	25.28 (24.79-25.78)
2007	25.95 (25.46-26.45)	16.20 (15.81-16.59)	4.53 (4.33-4.74)	32.12 (31.57-32.67)
2008	27.68 (27.18-28.18)	17.75 (17.35-18.14)	4.92 (4.71-5.13)	37.87 (37.29-38.45)
2009	31.01 (30.47-31.54)	20.10 (19.67-20.53)	5.81 (5.57-6.04)	46.54 (45.89-47.20)
2010	32.57 (32.01-33.12)	21.88 (21.43-22.33)	6.16 (5.92-6.40)	52.71 (52.01-53.41)
APC (95%CI)	13.85 (12.40-15.30)*	16.22 (14.70-17.80)*	17.60 (16.00-19.20)*	22.19 (21.20-23.20)*

*Annual percent change (APC) with 95% confidence intervals statistically significant at $p \leq 0.05$

3.5.4 Prevalence of strong opioid users according to drug and formulation

The prevalence of users prescribed each of the strong opioids (fentanyl, morphine, buprenorphine and oxycodone) and who received greater than 90 days' supply was determined over time. In 2000, most users who received greater than 90-days' supply were prescribed morphine, 4.62 (95%CI: 4.37, 4.87) per 10,000 person-years; and while the prevalence of morphine users fluctuated throughout the study period, by 2010 this had decreased to 1.78 (95%CI: 1.65, 1.91) per 10,000 person-years (Table 3-5).

Meanwhile, the prevalence of users who received fentanyl, buprenorphine and oxycodone >90 days per year continued to rise throughout the 11-year period by 15.89% (95%CI: 10.00, 22.10, p<0.001), 36.51% (95%CI: 17.80, 58.10, p<0.001) and 20.00% (95%CI: 13.70, 26.60, p<0.001) per year, respectively. By 2010, more long-term users were prescribed fentanyl and buprenorphine than morphine and oxycodone (Table 3-5).

Table 3-5 Annual prevalence of long-term users according to the four strong opioids

	Prevalence/10,000 person-years (95%CI)			
Year	**Fentanyl**	**Buprenorphine**	**Oxycodone**	**Morphine**
2000	1.20 (1.07-1.33)	1.57 (1.42-1.71)	0.10 (0.06-0.14)	4.62 (4.37-4.87)
2001	0.69 (0.59-0.78)	0.23 (0.17-0.28)	0.22 (0.17-0.27)	1.62 (1.48-1.76)
2002	0.99 (0.89-1.10)	0.37 (0.31-0.44)	0.30 (0.24-0.36)	1.46 (1.34-1.59)
2003	1.32 (1.20-1.44)	0.65 (0.57-0.73)	0.38 (0.32-0.45)	1.60 (1.47-1.73)
2004	1.56 (1.43-1.68)	0.77 (0.69-0.86)	0.47 (0.40-0.54)	1.61 (1.48-1.74)
2005	2.30 (2.15-2.46)	0.87 (0.78-0.96)	0.50 (0.43-0.57)	1.36 (1.24-1.47)
2006	2.76 (2.60-2.92)	3.14 (2.97-3.32)	0.56 (0.49-0.63)	1.61 (1.49-1.74)
2007	3.03 (2.86-3.20)	4.58 (4.37-4.79)	0.65 (0.57-0.73)	1.79 (1.66-1.92)
2008	3.18 (3.01-3.35)	5.51 (5.29-5.74)	0.63 (0.56-0.71)	1.77 (1.64-1.89)
2009	3.02 (2.85-3.19)	6.44 (6.20-6.69)	0.89 (0.80-0.98)	1.76 (1.63-1.89)
2010	3.00 (2.83-3.17)	7.03 (6.77-7.29)	0.90 (0.81-0.99)	1.78 (1.65-1.91)

An estimated 68.22% of strong opioid users who received greater than 90 days' supply in 2000 received long-acting preparations. By 2010, this had increased to 84.99% of users. In contrast, in 2000, the majority (52.22%) of users who received less than 90 days (short-term users) of strong opioids were prescribed short-acting formulations. However, by 2010, 58.58% of short-term users were prescribed long-acting strong opioids, suggesting a parallel shift in the type of strong opioid preparations used, similar to the alterations observed amongst long-term users (Table 3-6).

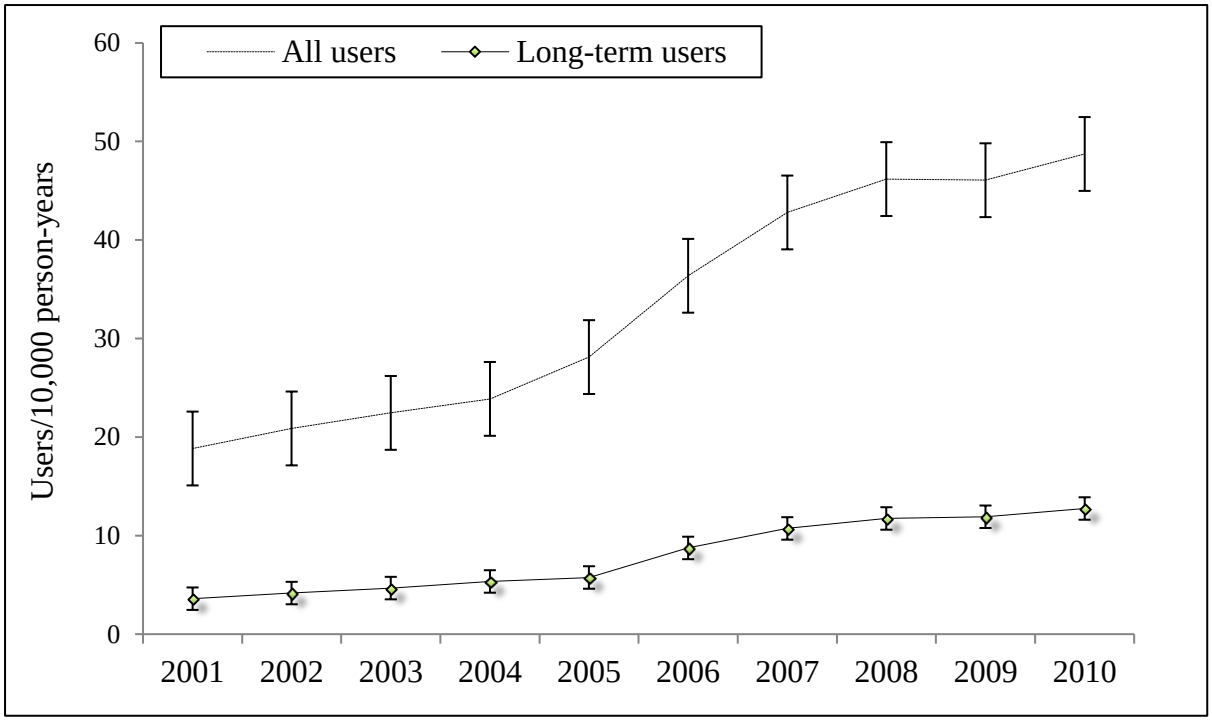
Table 3-6 Proportion of users prescribed long-acting and short-acting formulations

	Short-term users		**Long-term users**	
Year	**Long-acting**	**Short-acting**	**Long-acting**	**Short-acting**
	N (%)	**N (%)**	**N (%)**	**N (%)**
2000	2,099 (47.78)	2,294 (52.22)	1,726 (68.22)	804 (31.78)
2001	2,565 (47.90)	2,790 (52.10)	2,384 (69.99)	1,022 (30.01)
2002	3,220 (49.30)	3,312 (50.70)	3,172 (70.99)	1,296 (29.01)
2003	3,940 (50.33)	3,888 (49.67)	4,204 (74.20)	1,462 (25.80)
2004	4,464 (50.89)	4,307 (49.11)	5,308 (75.30)	1,741 (24.70)
2005	5,790 (52.20)	5,301 (47.80)	6,520 (76.21)	2,035 (23,79)
2006	8,066 (56.80)	6,135 (43.20)	9,123 (79.38)	2,370 (20.62)
2007	10,015 (58.34)	7,151 (41.66)	12,104 (81.10)	2,820 (18.90)
2008	11,485 (59.04)	7,968 (40.96)	15,153 (82.70)	3,170 (17.30)
2009	12,425 (59.02)	8,627 (40.98)	18,070 (83.79)	3,495 (16.21)
2010	13,072 (58.58)	9,241 (41.42)	20,503 (84.99)	3,621 (15.01)

3.5.5 Incidence of strong opioid prescription users

The incidence of strong opioid prescribing showed similar trends to the prevalence prescribing of the drugs over the 11 years of the study period (Table 3-7). The annual incidence of strong opioid users increased initially by 9.80% (95%CI: 6.50, 13.20) per year, from 18.84 (95%CI: 18.34, 19.34) per 10,000 person-years in 2001 to 28.12 (95%CI: 27.59, 28.65) per 10,000 person-years in 2005. The trend continued to rise steeply thereafter, but started to level off between 2008 and the end of the study in 2010. The incidence of strong opioid prescribing at the end of the study period was 48.73 (95%CI: 48.06, 49.40) per 10,000 person-years.

Figure 3-7 Annual incidence of strong opioid users, 2000-2010.



3.5.6 Incidence of strong opioid users according to day's supply

Analysis of the incidence of long-term (>90 days) strong opioid prescribing showed that approximately 16.96% (95%CI: 13.70, 20.30) of new non-cancer pain patients were prescribed strong opioids long-term annually over the 11 years (Figure 3-7). Notably, between 2005 and

2010, the incidence of long-term users doubled from 5.75 (95%CI: 5.51, 5.99) per 10,000 person-years to 12.75 (95%CI: 12.41, 13.10) per 10,000 person-years. In terms of the type of strong opioid prescribed, most long-term incidence users in 2001 received morphine: 2.46 (95%CI: 2.28, 2.64) per 10,000 person-years. By 2010, this had altered, and more long-term incidence users received buprenorphine: 6.52 (95%CI; 6.27, 6.76) per 10,000 person-years, which was twice as many morphine users and four-times as many fentanyl and oxycodone users (Table 3-7).

Table 3-7 Annual incidence of long-term users according to the four strong opioids

	Incidence/10,000 person-years (95%CI)			
Year	**Fentanyl**	**Buprenorphine**	**Oxycodone**	**Morphine**
2001	0.54 (0.45-0.62)	0.27 (0.21-0.33)	0.34 (0.27-0.40)	2.46 (2.28-2.64)
2002	0.82 (0.72-0.92)	0.44 (0.36-0.51)	0.46 (0.38-0.53)	2.46 (2.28-2.63)
2003	0.97 (0.86-1.07)	0.67 (0.58-0.75)	0.56 (0.48-0.64)	2.48 (2.31-2.64)
2004	1.23 (1.11-1.34)	0.84 (0.75-0.93)	0.74 (0.65-0.82)	2.54 (2.38-2.71)
2005	1.71 (1.58-1.84)	0.89 (0.79-0.98)	0.86 (0.77-0.96)	2.29 (2.14-2.44)
2006	2.09 (1.95-2.23)	3.06 (2.89-3.24)	0.91 (0.81-1.00)	2.69 (2.53-2.85)
2007	2.28 (2.14-2.43)	4.36 (4.15-4.56)	1.04 (0.94-1.14)	3.05 (2.88-3.22)
2008	2.13 (1.99-2.28)	5.41 (5.19-5.64)	1.12 (1.02-1.22)	3.07 (2.90-3.25)
2009	1.76 (1.63-1.88)	5.80 (5.57-6.03)	1.36 (1.25-1.47)	2.99 (2.83-3.16)
2010	1.66 (1.54-1.78)	6.52 (6.27-6.76)	1.45 (1.33-1.56)	3.13 (2.96-3.30)

Three quarters (75.15%) of new users of long-term strong opioids at the beginning of the study period received long-acting strong opioids. This continued to be a common practice in 2010, with 84.24% of long-term incidence users being prescribed long-acting strong opioids (Table 3-8).

Table 3-8 Long-term incidence users prescribed long-acting and short-acting formulations

Formulation	2001, N (%)	2010, N (%)	Annual percent change (95%CI)
Long-acting	774 (75.15)	4425 (84.24)	23.85 (19.40-28.40)*
Short-acting	256 (24.85)	828 (15.76)	13.82 (10.80-17.00)*

*Annual percent change (APC) with 95% confidence intervals statistically significant at $p \leq 0.05$

New users in 2001 who were prescribed ≤30 days were more likely to receive short-acting preparations of strong opioids (58.45%), whereas new users who were prescribed >90 days were likely to receive long-acting strong opioids. This pattern had not changed in 2010. Recipients of long-acting formulations were particularly common amongst new users using strong opioids between 91-120 days and in users supplied greater than 120 days of the potent opioids in a year (Table 3-9).

Table 3-9 Proportion of incidence users according to formulations used and total day's supply

	2001		2010	
Days' supply	Long-acting	Short-acting	Long-acting	Short-acting
	N (%)	N (%)	N (%)	N (%)
1-30	1,252 (41.55)	1,761 (58.45)	4,652 (48.40)	4,959 (51.60)
31-90	838 (62.17)	510 (37.83)	3,911 (75.08)	1,298 (24.92)
91-120	205 (70.69)	85 (29.31)	1,032 (80.88)	244 (19.12)
>120	567 (76.62)	173 (23.38)	3,394 (85.34)	583 (14.66)

3.6 Discussion

3.6.1 Main findings

The results of this study have confirmed a universal growth in the trend of strong opioid prescriptions written over an 11-year period nationally. This indicated a wide utilisation of the four strong opioids in non-cancer pain patients that was not limited to one UK geographic country.

The study has also demonstrated a consistent and steady increase in the overall incidence and prevalence prescribing of the four strong opioids in non-cancer pain patients in primary care. Importantly, there were significantly large increases in the incidence and prevalence of strong opioids prescribed over 90 days per year, which was used to define long-term opioid therapy. The incidence of long-term strong opioid use per 10,000 person-years between 2001 and 2010 was found to have almost doubled, suggesting a pattern of non-cancer patients exposed to the potent analgesics over prolonged periods.

Additionally, the increased rates of prescribing, particularly amongst patients prescribed >90 days' supply, appeared to have been driven mainly by increases in the prescribing of buprenorphine and oxycodone, which had greater annual percent change.

Long-acting preparations of strong opioids were consistently the most common formulations of strong opioids prescribed amongst prevalence and incidence users. In particular, long-acting formulations were increasingly common amongst new users using strong opioids between 91-120 days and greater than 120 days in a year.

3.6.2 Prevalence and incidence rates of prescribing

The increase in the annual volume of prescriptions of strong opioids issued over the study period can be attributed to a population effect, where the number of prescriptions increased in parallel with an expansion in the overall and the incident rates of medication users, with added contributions of cases of prolonged strong opioid users.

This population effect has been reported in few previous studies. A cross-sectional study published in 2014 reported a continuous rise in the annual prevalence of non-cancer pain patients using strong opioids from 1.8 per 1000 (equivalent to 18 per 10,000) to 9.2 per 1000 (92 per 10,000) patients registered in CPRD [(216)]. Although this was consistent with the findings of the current study, the findings were estimated without reference to durations of use.

Chevalier P et al. (2014) also used CPRD to examine the utilisation pattern of opioids between 2006 and 2011 [(218)]. The number of days of prescription use (and prior to possible discontinuation) was used as a primary outcome measure and patients were categorised as acute users if they had a total number of days' of drug supply of ≤30 days, sub-acute users if they had 31-182 days and chronic users if they had >183 days. Prevalence of chronic use over the 5-years was one in five, and unlike the current study the amount used by the users was found to reduce over time, suggesting a unique reduction in drug exposure.

Notably, findings of the present study demonstrated a sharp rise in strong opioid prescribing beyond 2005. This could potentially have been due to the increased availability of a number of strong opioid drugs and drug formulations at this time and beyond. Indeed, buprenorphine 7-day patch was made available in 2005, fentanyl 12mcg patch was also licensed in 2005, oxycodone with naloxone 10mg/5mg and 20mg/10mg (Targinact) was available after 2008,

and oxycodone with naloxone 5mg/2.5mg and 10mg/5mg in 2009 [253-255]. Furthermore from the periods 2002 and 2009, a number of prescribing guidelines and updates on analgesic use from the National Institute for Health and Clinical Excellence (NICE) and the Medicine and Healthcare product Regulatory Agency (MHRA) were produced, which may further explain the patterns observed in the current study [55, 256, 257].

The MHRA, which is a government regulatory organization that works closely with NICE, provides information on the safety and quality standards of different medicinal products to safeguard the publics' health [258]. In 2004, the MHRA released a safety report that advised on the avoidance of a number of NSAIDs due to their increased risk of cardiovascular events such as heart attack and stroke [256]. The advice was initially in relation to selective Cox-2 inhibitors; however, following reviews of evidence relating to the safety of NSAIDs, in 2006, the MHRA extended its safety message to include a cautionary use of non-selective NSAIDs, due to their increased risks of thrombotic events [259] . The advice to general practitioners was to tailor the dose according to patients' risk profile and to keep doses to the minimum effective level.

Interestingly, a longitudinal study by Bedson J et al. (2013) examined the impact of the MHRA guidance on GPs' prescribing behavior by studying the trend of analgesic prescribing in the years prior to and after the safety advice on NSAIDs (i.e. 2002-2009) [214].The study found a rapid decrease in the proportion of patients newly prescribed Cox-2 inhibitors and NSAIDs-excluding Cox-2 following the release of MHRA guidance, while at the same time there was an increase in the prescribing of weak and strong opioids, similar to the increased pattern in the prescribing observed in the current study. However, in the present study, the sharp increase in the prescribing was followed by stagnation in the incidence of strong opioid prescribing after 2008 until the end of the study in 2010. This trend coincided with the release of NICEs'

osteoarthritis (OA) guidelines in 2008 [55]. The new guidance recommended and encouraged the use of non-opioid medications before opioid analgesics, and it specifically advocated for the use of topical NSAIDs as a first line pharmacological treatment strategy prior to oral NSAIDs. Bedson J et al. (2013), who examined analgesic prescribing rates following the MHRA safety interjection, also investigated the effects of OA NICE guidance and demonstrated an unsurprising sharp rise in the prescribing of topical NSAIDs around and beyond the time of the guidance. At the same time, Bedson and colleagues (2013) showed a flattening in the prescribing of both weaker and stronger opioids [214].

Uniquely, the current study has demonstrated greater annual changes in the prescribing of buprenorphine. Although reasoning for this may be less clear, buprenorphine preparations exist in lower strengths, particularly as low-strength transdermal patches, which may make them more favourable for dose titrations in, for example, elderly patients and in cases where the oral route is restricted or difficult [260]. Likewise oxycodone prescribing rose more rapidly than any of the other strong opioids examined over the 11-years. Though it has been highlighted that oxycodone presents a slightly better pharmacokinetic profile than morphine in providing higher oral bioavailability (>60% of active drug reaches the systemic circulation versus 20-40% of morphine) and half-life (3-4hrs versus 2-3hrs with morphine); however, studies have indicated that the same reasons for its favourable traits in pain management makes it also liable for misuse, especially when introduced intranasally [261-263].

Findings in the present study suggested that the trend in strong opioid use was concentrated in long-acting formulations. A limited number of studies have compared short-acting and long-acting opioids in non-cancer pain, and most data regarding opioid efficacy have compared the active drugs with placebo control [153, 264, 265]. Nevertheless, a large systematic review, which

included 16 randomized trials and 8 observational studies, investigated the comparative efficacy profiles of long-acting opioids in non-cancer pain, and provided an overall sample size of 2,500 patients. The review concluded that there was inadequate evidence to demonstrate that long-acting opioids was superior in efficacy to short-acting opioids [153].

A few other studies have suggested concerns with prolonged use of long-acting opioid preparations. Common opioid-related adverse effects have been reported to occur less frequently with the use of short-acting opioids compared to long-acting formulations, such as bowel-related adverse events, nausea and vomiting [266, 267]. In addition, research has reported that long-acting opioids are associated with increased risk of unintentional overdose compared to short-acting or immediate release opioids, and the risk has particularly been observed in patients who were opioid-naïve prior to the use of long-acting opioid treatment [268, 269].

In more recent years, studies have increasingly focused on the examination of GPs' outlook on opioid use in CNCP, which provides an insight into the prescribing practice of primary care physicians and, in turn, could perhaps further explain the overarching upward trends in opioid prescribing in the present study [270-273]. Hutchinson K et al. (2007) carried out a large sample sized study in which 115 primary care physicians completed an in-depth questionnaire, which included questions about their current prescribing patterns of opioids in chronic non-cancer pain, their views on opioid use for CNCP, and the level of pain management training and experience they had [270].

Factor analysis was used in the study to determine the association between beliefs/views and prescribing patterns and the study found that opioid prescribing was mainly predicted by a belief that opioids were appropriate in CNCP, yet only 11% of the study's participants reported to have had specialised training in pain management. Similarly, in a different study Blake H et

al. (2015) found that 72.7% of the GPs surveyed prescribed strong opioids for CNCP and it was reported that more than half of the GPs surveyed felt that there were frequently no pharmacological alternatives in CNCP other than opioids [271].

A further study by Gooberman-Hill R et al. (2011) used face-to face interviews with GPs to determine physicians' views on opioid prescribing for joint pain [273]. The study found that a prior experience with strong opioid prescribing was a significant influencer in prescribers' current opioid prescribing, with physicians who did not prescribe opioids in joint pain attributing this to a lack of prior experience. However, disconcertingly, the study found that physicians who prescribed strong opioids for joint pain referenced their experience of prescribing the drugs to in palliative care.

3.6.3 Prescribing trends compared to international studies

The longitudinal changes in strong opioid prescribing observed in the current study are comparable to patterns described in several studies conducted in the United States, Canada, Australia and Europe.

A large US study by Boudreau D et al. (2009) examined data obtained from two national healthcare insurance plans (Group Health and Kaiser Northern California), which collectively provide healthcare coverage to approximately 4 million persons in the United States (1% of the US population). The study assessed yearly long-term use of opioids (long-term use was defined as ">90 days with 120+ days' supply or 10+ opioid prescriptions in a given year") in adults with non-cancer pain from 1997 to 2005 [274]. Comparable to the current study, Boudreau D et al. (2009) calculated the annual percent change (PCA) of medication use and found that

the overall utilisation of long-term opioids grew by 8.1% and 8.6% respectively in each of the healthcare plans, and from 23.9 to 46.8 per 1000 and from 21.5 to 39.2 per 1000, respectively.

Over the same period the study found that the annual percent change of the incident of long-term opioid use also rose by 6.0% (95%CI; 5.4, 6.5) and 5.5% (95%CI: 5.3, 5.7) respectively, and there was a substantial growth in the use of stronger opioids long-term, more so in the Kaiser Permanente's insured patients (short-acting Schedule II: 10.0 PCA and long-acting Schedule II: 12.9 PCA) [(274)]. Meanwhile, Kuo YF et al. (2016) reported that between 2007 and 2012, the proportion of patients who were enrolled in the US' healthcare insurance program Medicare and who received long-term opioids increased nationally from 1.42% to 2.24% for schedule I drugs and 3.42% to 5.46% for schedule II drugs, denoting a continuous ascending trend [(275)].

Likewise, a Canadian study by Smolina K et al. (2016) demonstrated an average annual rise of 2.76% (95%CI 2.06–3.46) of long-term opioid users from 2005 to 2012, or a prevalence increase from 14.4 per 1000 men and 17.8 per 1000 women in 2005 to 18.3 per 1000 men and 21.7 per 1000 women in 2012 [(276)]. The same study found that oxycodone together with morphine was amongst the most repeatedly prescribed opioid long-term. Similarly, Berecki-Gisolf J et al. (2017) captured trends in the dispensing of opioid prescriptions in Australia from 2006 to 2013 and calculated the average annual change in opioid use per 100 residents [(277)]. The study reported an average APC of 38% (0.9-0.6), 27% (0.5-2.3), 16% (6.1-17.3) and 6.4% (4.1-2.5) for buprenorphine, fentanyl, oxycodone and morphine respectively. Like Smolina K et al. (2016) the study noted a difference in opioid use by age and gender and found that oxycodone prescribing were more frequent in woman and in persons aged ≥65 years [(277)].

In the Nordic countries, a recent Norwegian study by Neutel CI et al. (2014) utilised a nationwide prescription database to examine the number of patients issued with one or more strong opioid prescriptions between 2005 and 2010 [278]. The study found that the number of strong opioid prescriptions filled grew annually by 60% over the 6-years from 138,821 in 2005 to 222,383 in 2010. Moreover, the rise was most prominent amongst patients aged >40 years, with 8.6 per 1000 of patients aged 40-80 years receiving strong opioids in 2005 to 13.3 per 1000 40-80 year olds in 2010. Furthermore, as in the present study, prescriptions of oxycodone increased more than any other strong opioid; however, it was not clear if the prescribing was for short-term or long-term use.

3.6.4 Strengths and limitations

This study has detected changes in the prevalence and incidence of non-cancer pain patient's prescribed strong opioids over time relative to the duration of days' supply, hence succeeding in estimating long-term prescribing over time. However, there are limitations contained within the analysis that merit description. Firstly, prescriptions were used as a proxy of estimating the use of strong opioids in primary care, with no source available within the database to indicate that the prescribed drug(s) were dispensed. Secondly, cancer diagnostic codes applied in the investigation were based on codes in the CPRD-dictionary as well as codes used in a previously published UK study and QOF codes, and not necessarily validated by the UK national cancer registration data. Hence, there may have been missed codes that were not picked up by the strategy used. Nevertheless, the compatibility of the recording of cancer diagnoses in CPRD with the Office for National Statistics for cancer registration data (ONS) have been shown to be relatively high (83.3%) [279].

Finally, in any analysis that aims to investigate changes in patterns of variable(s) over time, risk factors affecting trends may need to be accounted for. In this initial study, crude estimations of prescribing were sought, and no demographic and clinical information was examined alongside the prescribing trends. However, this is overcome in subsequent chapters, which analyses treatment patterns over time while taking into account a number of covariates, including demographic and clinical variables.

3.6.5 Conclusions

This study presented information on changes in the prescribing activity of four strong opioids. Accordingly, a growing prevalence and incidence of non-cancer pain patients utilising strong opioids long-term, which was a total use of greater than 90 days per year, between 2000-2010 were identified. This warrants a continued need for vigilance and attentiveness, and merits further investigations in order to understand the types of patients selected for strong opioid treatment and a detailed examination into the patterns of consumption.

Chapter 4 Characteristics of non-cancer pain patients prescribed strong opioids and traits of recipients of long-term therapy

4.1 Introduction

Recent cohort studies conducted outside the UK have suggested that opioid utilisation, particularly that of long-term use, is observed in subgroups of non-cancer pain patients who may be characterised by constellations of multiple and complex physical and psychological morbidities [280-282]. For instance, a population-based cohort study in Norway found that among chronic non-cancer pain patients prescribed persistent opioids, 85% had at least one general medical comorbidity, and almost 1 in 2 had three or more somatic co-morbidities in which opioids would generally be contraindicated (severe obstructive airways diseases, chronic liver disease) [283]. Another study found that psychiatric disorders were prevalent in patients prescribed long-term opioids compared to their counterparts of patients not prescribed opioids [280].

Patients with comorbid factors may be at higher risk of poorer health outcomes due to the additional range of health and non-health related factors. In addition, patients with factors such as advanced age, cardiovascular, respiratory, renal, hepatic or mental disorders have an increased susceptibility to adverse events with opioid use due to deleterious drug-organ system–based interactions [174, 184, 185, 284, 285]. For this reason, patients with predisposing comorbid factors have generally been excluded from clinical trials of opioid efficacy and safety, and the extent of opioids' effectiveness in these patients remains less understood [286].

Opioid treatment guidelines have highlighted vigilant assessment and careful selection of patients for long-term opioid use [116, 287-289]. Commonly, long-term opioid therapy is recommended for patients with intractable pain and cautionary prescribing and use have been emphasized in patients with history of psychiatric disorders, the elderly, and in patients with

serious medical morbidities. Although a few studies conducted in UK primary care have examined the socio-demographics of non-cancer pain patients prescribed opioids, analysis of medical diagnostic traits, particularly in users of stronger opioids and those on long-term treatment, have seldom been the primary focus of previous studies.

Recently, Foy R et al. (2016) examined patient-level prescribing of opioids in practices throughout Leeds and Bradford between 2005 and 2012 and found that a stepping up of prescribing to strong opioids was mostly observed in females and in the age group of 65-100 years [(215)]. In contrast, a prospective postal survey study in North Staffordshire by Green DJ et al. (2013) found that neither gender nor older age were significant in strong opioid prescription use [(219)]. Ruscitto A et al. (2015), on the other hand, assessed opioid prescribing in the Tayside region of Scotland, and found that socioeconomic deprivation and polypharmacy were the main factors associated with the receipt of strong opioids [(213)].

Knowledge about clinical traits is important in understanding key factors for patient illness, and is also crucial when considering long-term opioid treatment where clinical information is acute for patient-selection. Obtaining information about patients who are exposed to stronger opioids, including prolonged treatments, would play an important role in informing practice about the health and extent of care that may be needed by the patients and thereby may facilitate appropriate treatment decisions and responses.

4.2 Aims and objectives

The aims of this study were to examine the characteristics of non-cancer pain patients prescribed strong opioids and identify traits of long-term users.

The objectives for this study were to:

1. Describe the socio-demographic (including age, gender, marital status, deprivation and lifestyle indicators) and clinical traits (pain conditions and co-existing morbidities) of non-cancer pain patients' prescribed strong opioids between 2000-2010.
2. Identify characteristics of non-cancer pain patients prescribed strong opioids long-term in any given year during the study period.

4.3 Methods

4.3.1 Study design

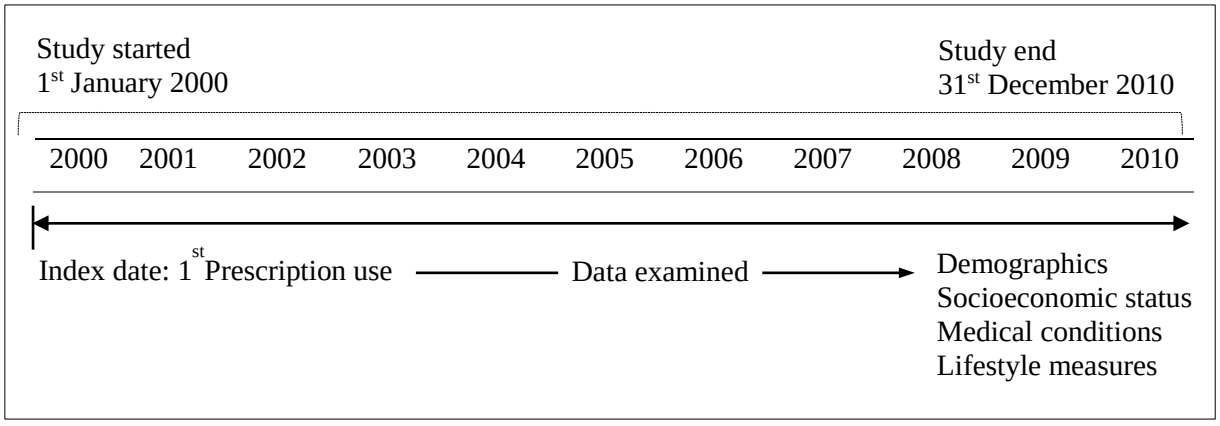
This study was a retrospective cross-sectional study of adult non-cancer pain patients prescribed strong opioids, using CPRD database, from January 2000 to December 2010 (Figure 4-1).

4.3.2 Study subjects

Adult patients identified in chapter 3 formed the basis of the study population in this chapter. These were made up of patients ≥18 years without cancer diagnosis 12 months within the date of their first strong opioid prescription. Patients had to have had one or more prescriptions between January 2000 and December 2010.

The patients' identification codes of strong opioid users examined in the previous chapter were used in the current study to extract demographic and clinical information. This was obtained from the following files in CPRD: practice, clinical, consultation, referral and additional (clinical details) file. Any records before the practice up-to-standard date (the date in which the practice data is deemed to be of good quality for research) or before patient registration date were excluded.

Figure 4-1 Outline of the study design



4.3.3 Study measures

4.3.3.1 Demographics and socioeconomic information

Demographic data that is routinely recorded within CPRD files include age, gender, region, marital status and socioeconomic status; these were identified and extracted. Age was calculated from the date of the patients' first strong opioid prescription and analysed as a categorical variable of five categories: 18-29 years, 30-49 years, 50-69 years, 70-79 years and ≥80 years. Marital status was measured following the patients' first prescription date and was analysed as: single, married, widowed, divorced, separated and other (engaged, co-habiting, re-married, stable relationship and civil relationship) as per recorded in CPRD.

Patients' practice region was also determined. Practices in England are available in the CPRD according to strategic health authority regions, and include: North East, North West, Yorkshire and Humber, West Midlands, East Midlands, East of England, South West, South Central, South East Coast, and London [229]. Strategic health authorities were part of the NHS in the UK that managed primary care trusts/NHS Trusts and help to oversee the implementation of health policies set by the Department of Health. Strategic health authorities were abolished in 2013 (31st of March) and were subsequently replaced by clinical commissioning groups [290].

Socioeconomic status was measured using Townsend deprivation index - 2001 census. The index is a commonly used measure of deprivation in health studies, and it consists of deprivation scores, which are calculated from four domains:

- Unemployment: percentage of unemployed individuals over 16 years of age who are economically active.
- Non-car ownership: percentage of all households not owning a car.
- Non-home ownership: percentage of all households not owning a home.

- Household overcrowding: percentage of households with more than 1 resident per room.

The scores for each domain are added to provide a total score and this is presented as ranks of 5 quintiles with 1 denoting least deprived and 5 as most deprived. The CPRD provides linkage to the Townsend score file through the patient file, and the scores were linked to patients in CPRD through patients' identification codes.

4.3.3.2 Clinical information

Medical information that was of interest and that was analysed in the study included pain disorders, general co-morbidities and lifestyle indicators. The generation of Read codes for pain conditions involved several steps. In the first stage, a list of pain conditions of interest was outlined. This was informed and based on a comprehensive list of defined pain conditions by the Classification of Pain Diseases Task Force of the International Association for the Study of Pain (IASP) [(1)] (Appendix 11). The IASP taskforce was developed in response to the need for unified definitions and categorisations of chronic pain conditions, and to create a classification system that could be used in primary care and in clinical settings (and included in the International Classification of Diseases (ICD) of the World Health Organization).

Read codes (and medical codes) for the corresponding pain conditions were obtained using the inbuilt medical browser in CPRD [(229)] (Appendix 11). Given that there may be multiple Read codes for a single condition that may appear under different diagnostic chapters such as the symptom chapter (R) or injury chapter (S and T), the list of Read codes had to be carefully reviewed to ensure that the codes corresponded to possible pain disorders (including musculoskeletal pain disorders) and the final list of codes was established through a consensus approach. Strong opioid patients that were diagnosed with one or more pain conditions were

subsequently identified from the clinical, referral and consultation files in CPRD, and only clinical diagnosis that was recorded after patients' first strong opioid prescription use were included for study.

General co-morbid conditions were determined using the Quality and Outcomes Framework (QOF). The QOF business rules defines long-term diseases as conditions that last 6 months or more and that require on-going disease or risk management [246]. QOF was designed to improve the monitoring and care of a defined number of common long-term diseases, and to remunerate general practices for their performance against a range of quality indicators formulated by the General Medical Services (GMS) contract. Read codes for 27 QOF long-term morbidities were applied to CPRDs' dictionary to obtain equivalent Read/medical codes, which were used to identify patients with the conditions from their clinical, referral and consultation files [246] (Appendix 12).

Psychiatric illnesses that have commonly been reported in primary care have included: (a) psychoses, (b) depression (c) anxiety, (d) schizophrenia, (d) paranoia, (e) neurosis, (f) personality/behavioural disorders/problems and (g) other disorders (insomnia, and hallucinations) [291, 292]. Read and medical codes of each of the mental and behavioural disorders were determined in CPRDs' dictionary using related search terms and applied to the clinical, referral and consultation files to identify patients with a clinical diagnosis of the disorder(s) (Appendix 13).

In terms of health-related lifestyle indicators, information on patients' smoking and alcohol consumption was identified in the clinical and additional files through the use of related medical codes and enttype codes. Patients' smoking and alcohol use status was determined

close to the date of their first prescription use over the study period (1st January 2000 to 31st December 2010). Smoking status was stratified as non-smoker, former smoker and as current smoker and alcohol consumption was defined as drinker (mild, moderate, heavy), non-drinker and ex-drinker. For users who had multiple different smoking and alcohol statuses recorded on the same date, their statuses were coded as unknown and managed as missing data.

All clinical diagnosis had to have been recorded after patients' first prescription date and within patients' registration date and up-to research standard date for inclusion and analysis.

4.3.4 Data management

All socio-demographic and clinical data were checked for missing values. It was found that 78.49% (n=106,705) of strong opioid users did not have a marital status recorded, 37.86% (n=51,462) were without a socioeconomic status, 40.19% (n=54,638) had no smoking status and 54.10% (n=73,547) had no alcohol status recorded (Table 4-1).

Table 4-1 Proportions of the study sample with missing socio-demographic data

	Marital status	**Townsend score**	**Smoking**	**Alcohol status**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Missing	106,705 (78.49)	51,462 (37.86)	54,638 (40.19)	73,547 (54.10)
Non-missing	29,236 (21.51)	84,479 (62.14)	81,303 (59.81)	62,394 (45.90)

4.3.4.1 Strategy for imputing missing socioeconomic records

Little, in 1998, described three mechanisms by which values in a dataset can be missing, and proposed a test to differentiate the mechanism [293]. Values could either be: missing completely at random (MCAR) and not dependent on the observed nor unobserved values; or the likelihood of values being missing could be dependent upon any of the observed variables in the dataset,

which could be used to predict the missing values, (missing at random, MAR); and the last alternative would be that the missing values could be solely dependent on the missing or unobserved measurements in the dataset (missing not at random, MNAR).

To test the pattern of missing data of marital status, Townsend score, smoking status and alcohol status binary variables were created with 1 indicating missing marital status, missing Townsend score, missing smoking and missing alcohol status, and 0 otherwise. Subsequently, logistic regression was preformed to test if the missing values were dependent on the rest of the observed variables in the dataset, which included age, gender, region, pain conditions, QOF morbidities and drug exposure. The binary variables were used as dependent variables, and the observed variables as the independent, in the analysis. As it is often difficult to establish which variables from the dataset to include in the regression model that is used to evaluate the patterns of missing data, Raghunathan and colleagues (2001) have shown that by maximizing the inclusion of more variables in the regression model of missing data can lead to diminished standard errors of estimates, and allow estimates to be more accurate [(294)]. Thus, as many of the available variables in the dataset were included.

Results from the logistic regression showed that the missing data were significantly associated with several observed variables in the dataset, as indicated by the *p*-values (Appendix 14). The likelihood of missing marital status was influenced by the following observed variables: age, gender, region, a number of specific pain and QOF morbidities, co-prescriptions with antidepressants and benzodiazepines. For Townsend score, it was: age, gender, region, certain pain conditions, and QOF morbidities, including psychiatric disorders, co-prescriptions with benzodiazepines. Missing records of smoking status and alcohol status were both correlated

with: age, gender, region, a few pain conditions and QOF morbidities, co-prescriptions with benzodiazepines, non-benzodiazepines and antidepressants (Appendix 14).

Multiple imputation method by chained equation for managing missing data proposed by Rubin DB et al. (1976) was used to impute the missing values [295] (Table 4-2). This involves developing more than one set of replacements for the missing values based on the associated predicted values (which is selected from the regression analysis described earlier) from the complete dataset. The statistical reasoning behind multiple imputations is that the observed data likelihood can be estimated by the average of the completed-data likelihood over unknown missing values. The method has the advantage of introducing random error into the imputation process which reflects the uncertainty associated with the parameters used to estimate the missing data and thus enables less biased estimates to be generated [249, 295, 296]. The imputation method was conducted with 10 cycles.

4.3.4.2 Imputation diagnostic

Once the imputations had been carried out, summary statistics were used to check the outcome and identify any discrepancies in the procedure (Table 4-3). Summary statistics of marital, Townsend scores, smoking and alcohol status showed that the distributions for the imputed and combined values were reasonable and not largely different from the observed data, which confirmed the consistency of the dataset (original dataset, not imputed).

Table 4-2 Results of multiple imputation of socio-demographic data

Numerical comparison of observed and imputed data						
Variable	**Observed**		**Imputed**		**Complete**	
	N	**%**	**N**	**%**	**N**	**%**
Marital	29,236	21.51	106,705	78.49	135,941	100
Townsend score	84,479	62.14	51,462	37.86	135,941	100
Smoking	81,303	59.81	54,638	40.19	135,941	100
Alcohol	62,394	45.90	73,547	54.10	135,941	100

Table 4-3 Imputation diagnostic: summary statistics of multiple imputed data

Numerical comparison of observed and imputed data					
Variable	**Numbers**	**Minimum**	**Maximum**	**Mean**	**SD**
Marital status					
Observed data (before imputation)	29,236	1	5	2.13	0.74
Complete data (after imputation)	135,941	1	5	2.12	0.74
Townsend score					
Observed data (before imputation)	84,479	1	5	2.85	1.33
Complete data (after imputation)	135,941	1	5	2.78	1.33
Smoking status					
Observed data (before imputation)	81,303	1	3	2.01	0.71
Complete data (after imputation)	135,941	1	3	1.99	0.71
Alcohol status					
Observed data (before imputation)	62,394	1	3	1.28	0.50
Complete data (after imputation)	135,941	1	3	1.28	0.50

4.4 Data analysis

4.4.1 Descriptive statistics

Descriptive analysis was used to initially report socio-demographic and diagnostic measures for all strong opioid users and subsequently describe the demographic and clinical characteristics of long-term users. A similar definition of long-term strong opioid use to that used in chapter 3 was adopted in this study; this was defined as users who had a sum total of >90 days' supply in at least one year during the study period, which ran from 1st January 2000 until 31st of December 2010.

Characteristic data was presented as frequency and percentage, and normally distributed continuous variables such as age were presented as mean (standard deviation), whereas categorical variables were presented as proportions. In addition, the percentage of users with multiple pain disorder was analysed in relation to demographic characteristics such as age, gender, Townsend deprivation etc., and the mean number of QOF long-term morbidities were also analysed relative to age, gender, deprivation score and number of pain diagnoses, and presented with 95% confidence intervals and standard deviation.

The analyses were conducted using STATA, version 14.0 (Stata Corporation, College Station, TX, USA).

4.5 Results

4.5.1 Strong opioid users' characteristics

The characteristics of the study sample (135,941 non-cancer pain patients prescribed strong opioids in primary care, 2000-2010) are shown in Table 4-4. The mean age was 66.34±17.98 years, and the largest proportions of users to receive strong opioids were patients between 50-69 years (31.05%) and those aged ≥80 years (27.76%). There were almost twice as many female users (63.64%) as male (36.35%) users over the 11-year period.

The majority of strong opioid users were married (67.69%), and the lowest number of users were either divorced (4.70%) or separated (1.31%). More than half of the patients had a deprivation quintile of ≥2, with 23.91%, 21.87% and 20.28% having quintiles of 2, 3 and 4, respectively. Approximately one in two of strong opioid users were non-smokers (49.09%), and one in four of users were either current smokers (25.50%) or ex-smokers (25.41%) (Table 4-4).

In addition to the information collected on smoking status, details about alcohol consumption were also obtained within users' first date of receiving strong opioid prescription. Amongst the study participants, 73.98% were drinkers (defined as mild, moderate or heavy alcohol intake), 23.71% were non-drinkers and 2.31% were former drinkers. Examination of the proportions of users by region showed that there were slightly greater numbers of strong opioid users in the North West (12.41%), South West (11.40%) and South Central (10.42%) than in any other English region.

Table 4-4 Socio-demographic characteristic of the study sample

Characteristics	N	%
Age (mean±SD, years)	66.34±17.98	
Age categories		
18-29 years	3,606	2.65
30-49 years	23,862	17.55
50-69 years	42,216	31.05
70-79 years	28,520	20.98
≥80 years	37,737	27.76
Gender		
Male	49,418	36.35
Female	86,519	63.64
Marital status		
Single	17,359	12.77
Married	92,013	67.69
Widowed	18,393	13.53
Divorced	6,390	4.70
Separated	1,786	1.31
Townsend deprivation score (Quantile)		
1 (least deprived)	28,962	21.30
2	32,508	23.91
3	29,726	21.87
4	27,570	20.28
5 (most deprived)	17,175	12.63
Smoking status		
Current smoker	34,664	25.50
Non-smoker	66,735	49.09
Ex-smoker	34,542	25.41
Alcohol intake status		
Drinker*	100,566	73.98
Non-drinker	32,234	23.71
Ex-drinker	3,141	2.31
Region		
England		
North East	2,946	2.17
North West	16,870	12.41
Yorkshire & Humber	5,224	3.84
East Midlands	4,711	3.47
West Midlands	12,652	9.31
East of England	11,273	8.29
South West	15,502	11.40
South Central	14,166	10.42
London	8,949	6.58
South East	13,006	9.57
Northern Ireland	6,937	5.10
Wales	13,340	9.81
Scotland	10,365	7.62

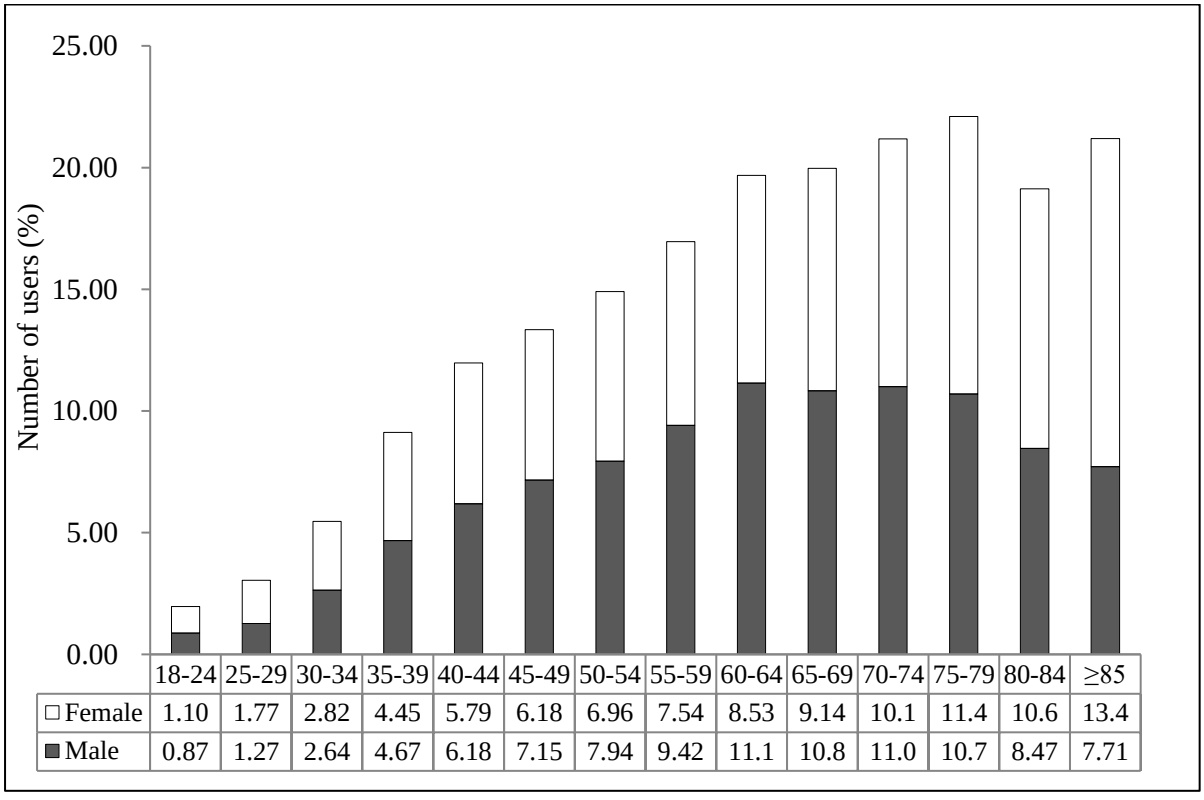
*Drinker= mild, moderate and heavy

4.5.1.1 Pain diagnoses and general comorbid conditions

Eighty-two percent (n=111,654) of the study population had a record of pain diagnosis during the study period. Of these, 17.60% (n=23,931) had one-pain condition, 17.43% (n=23,695) had 2 conditions and 47.10% (n=64,028) had 3 or more pain disorders. The most common pain diagnoses were back pain (48.47%), abdominal pain (34.65%), thoracic pain (30.79%), osteoarthritis (26.70%), shoulder pain (26.50%) and neck pain (23.99%) (Table 4-8).

There were age and gender differences observed in the proportions of pain conditions diagnosed. Sixty percent of males (n=29,718) and 67.04% (n=58,005) of females had a record of two or more pain disorders (Figure 4-2). For males, the frequencies of having two or more pain conditions peaked at 11.15% in the 60-64-year old age-group, and the presence of multiple pain disorders was generally greater in this age group.

Figure 4-2 Proportion of users with two or more pain conditions, by age and gender



	18-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85
□ Female	1.10	1.77	2.82	4.45	5.79	6.18	6.96	7.54	8.53	9.14	10.1	11.4	10.6	13.4
■ Male	0.87	1.27	2.64	4.67	6.18	7.15	7.94	9.42	11.1	10.8	11.0	10.7	8.47	7.71

For females, the occurrence of two or more painful conditions peaked at 13.47% in the oldest age group (≥85 years), and the occurrence of multiple pain disorders was generally more common in patients aged 60 and over compared to users aged under 60.

In terms of general morbidities, 77.27% (n=105,038) of the users had one or more long-term conditions included in the QOF, 50.82% (n=69,087) had two or more, and 30.33% (n=41,236) had three or more QOF conditions. Table 4-5 demonstrate that multimorbidity was strongly related to age, with 77.92% of users aged 50-69 having an average of two morbidities, whereas 84.40% of users aged 70-79 had an average of 3 morbidities. Multimorbidities were also more common in females, in users with higher deprivation scores, and in users with greater numbers of pain conditions (Table 4-5).

Table 4-5 Proportions of strong opioid users with record of (QOF) co-morbidities

Characteristics	**N (%)**	**Mean no of QOF morbidities**	**Percentage (95%CI) with QOF morbidities**
Gender			
Male	49, 418 (36.35)	2.39 (1.51)	73.77 (73.01-74.52)
Female	86 519 (63.64)	2.47 (1.52)	79.27 (78.67-79.86)
Age, years			
18–29	3,606 (2.65)	1.49 (0.86)	57.38 (54.90-59.85)
30–49	23,862 (17.55)	1.75 (1.05)	65.16 (64.13-66.18)
50–69	42,216 (31.05)	2.38 (1.46)	77.92 (77.08-78.77)
70–79	28,520 (20.98)	2.80 (1.62)	84.40 (83.33-85.46)
≥80	37,737 (27.76)	2.65 (1.57)	80.70 (79.80-81.61)
Townsend score (Quintile)			
1 (affluent)	28,962 (21.30%)	2.26 (1.42)	43.36 (42.36-44.36)
2	32,508 (23.91%)	2.28 (1.41)	44.25 (43.32-45.18)
3	29,726 (21.87%)	2.32 (1.43)	45.56 (44.59-46.52)
4	27,570 (20.28%)	2.36 (1.48)	46.32 (45.31-47.32)
5 (deprived)	17,175 (12.63%)	2.45 (1.53)	47.96 (46.70-49.23)

(Continued) Table 4-5 Proportions of strong opioid users with record of co-morbidities

Characteristics	N (%)	Mean no of QOF morbidities	Percentage (95%CI) with QOF morbidities
Pain disorders			
0	24,287 (17.87)	1.87 (1.15)	57.69 (56.73-58.64)
1	23,931 (17.60)	2.15 (1.33)	71.81 (70.74-72.88)
2	23,695 (17.43)	2.33 (1.42)	77.66 (76.54-78.78)
3	20,862 (15.35)	2.50 (1.52)	82.21 (80.98-83.44)
4	16,490 (12.13)	2.63 (1.58)	85.52 (84.11-86.93)
≥5	26,676 (19.62)	2.92 (1.69)	90.68 (89.54-91.82)

Hypertension, asthma, coronary heart disease, coronary kidney disease and diabetes were the most common comorbidities amongst strong opioid users, followed by osteoporosis and chronic obstructive pulmonary disease, of which an equal number of users had the conditions (Table 4-9).

In terms of mental health related morbidities examined, depression and anxiety were a common presentation and prevalent in 43.52% and 19.70% of strong opioid users, respectively (Table 4-6). Furthermore, the conditions were more prevalent in females, with depression recorded in 44.20% and anxiety in 22.18% of female users, respectively.

Table 4-6 Proportions of strong opioid users with psychiatric disorder(s)

Psychiatric disorder	All users	Female users	Male users
	N (%)	N (%)	N (%)
Depression	59,163 (43.52)	38,240 (44.20)	20,923 (42.34)
Anxiety	26,774 (19.70)	19,191 (22.18)	7,583 (15.34)
Personality disorder	1,152 (0.85)	734 (0.85)	418 (0.85)
Insomnia/hallucination	244 (0.18)	160 (0.18)	84 (0.17)
Psychosis	158 (0.12)	112 (0.13)	46 (0.09)
Paranoia	133 (0.10)	85 (0.10)	48 (0.10)
Neurosis	138 (0.10)	103 (0.12)	35 (0.07)
Schizophrenia	77 (0.06)	39 (0.05)	38 (0.08)

4.5.2 Characteristics of users receiving long-term strong opioids

Overall, 32.35% (n=43,972) of the study population had a total days' supply of greater than 90 days in at least one year of the study period. Long-term users' demographic and clinical traits are shown in Table 4-7, Table 4-8 and Table 4-9. Most of the long-term users were females (65.57%), the average age was 64.52±17.08 years, and greater proportions of them were between 50-69 years (34.83%) of age.

Table 4-7 Characteristics of users prescribed strong opioids long-term in a year

Long-term users	**N**	**%**
Age (mean±SD, years)	64.52±17.08	
Age categories		
18-29 years	897	2.04
30-49 years	8,607	19.57
50-69 years	15,316	34.83
70-79 years	9,215	20.96
≥80 years	9,937	22.60
Gender		
Male	15,140	34.43
Female	28,832	65.57

Long-term users were found to have a mean number of pain diagnoses of 3.0±2.2, and more than half (54.87%, n=15,820) of female long-term users had three or more pain conditions.

Similarly, co-existing long-term QOF morbidities were common among long-term users; almost 1 in 2 (55.11%, n=24,233) had two or more long-term co-morbidities recorded. Hypertension was frequent in 23.80% of long-term users, asthma in 19.12%, coronary heart disease in 17.84% and chronic kidney disease in 17.02% of long-term users. The proportion of long-term users with depression was 50.02%, and anxiety occurred in 22.13% of long-term users (Table 4-9).

Table 4-8 Type of pain conditions among strong opioid users

	All users, N (%)	**Long-term users, N (%)**
Pain conditions*	**(N=135,941)**	**(N=43,972)**
Back pain	65,896 (48.47)	23,846 (54.23)
Abdominal pain	47,099 (34.65)	15,859 (36.07)
Thoracic/chest pain	41,852 (30.79)	14,603 (33.21)
Osteoarthritis	36,291 (26.70)	13,269 (30.18)
Shoulder pain	36,027 (26.50)	12,634 (28.73)
Neck pain	32,613 (23.99)	11,162 (25.38)
Headache	27,714 (20.39)	9,384 (21.34)
Sciatica	23,156 (17.03)	7,870 (17.90)
Neuropathy	5,985 (4.40)	2,663 (6.06)
Migraine	7,381 (5.43)	2,579 (5.87)
Fibromyalgia	3,186 (2.34)	1,438 (3.27)
“Others”	47,397 (34.87)	17,294 (39.32)
Number of diagnosis		
1	23,931 (17.60)	7,392 (16.81)
2	23,695 (17.43)	7,732 (17.58)
>3	64,028 (47.10)	22,840 (51.94)
Mean±SD	2.66±2.15	3.00±2.16

*Users may have multiple pain conditions recorded

Table 4-9 Type of long-term comorbidities among strong opioid users

	All users, N (%)	**Long-term users, N (%)**
Medical comorbidity*	**(N=135,941)**	**(N=43,972)**
Hypertension	30,792 (22.65)	10,466 (23.80)
Asthma	23,213 (17.08)	8,406 (19.12)
Coronary heart disease	22,835 (16.80)	7,845 (17.84)
Chronic kidney disease	21,276 (15.65)	7,486 (17.02)
Diabetes	16,692 (12.28)	6,111 (13.90)
Osteoporosis	13,555 (9.97)	5,325 (12.11)
Chronic obstructive pulmonary disease	12,344 (9.08)	4,281 (9.74)
Stroke	11,792 (8.67)	3,655 (8.31)
Heart failure	11,019 (8.11)	3,373 (7.67)
Atrial fibrillation	10,430 (7.67)	3,099 (7.05)
Hypothyroidism	9,867 (7.26)	3,575 (8.13)
"Others"	25,092 (18.46)	8,898 (20.22)
Mean±SD	1.89±1.68	2.04±1.70
Psychiatric disorder	**All users, N (%)**	**Long-term users, N (%)**
Depression	59,163 (43.52)	21,994 (50.02)
Anxiety	26,774 (19.70)	9,730 (22.13)
"Others"	1,902 (1.40)	668 (1.52)

*Users may have multiple co-morbidities recorded

4.6 Discussion

4.6.1 Main findings

This study had the main goal of examining the socio-demographic profile of a sample of non-cancer pain patients prescribed strong opioids in primary care, and to investigate the extent and range of long-term morbidities that the users had.

Overall, the results showed that the majority of patients prescribed strong opioids were females and over the age of 50. The most common pain syndromes recorded were back pain, osteoarthritis, shoulder and neck pain. Even though a majority of the users had a record of pain condition, it was not possible to determine which condition(s) strong opioids had been prescribed for.

Almost half of the users had two or more comorbidities co-existing with their pain, and common long-term conditions were related to the cardiovascular (e.g. hypertension, coronary heart disease), respiratory (asthma and chronic pulmonary obstructive disease) and the renal (coronary kidney disease) systems. It was also evident that female users, those with an increased age, and users who were highly deprived were more likely to have greater mean numbers of long-term co-morbidities.

An estimated 1 in 3 of the users had received long-term strong opioid supply, which was defined as a total supply of greater than 90 days in any one year during the study period. These users were characterized by a number of pain and co-morbid illnesses; half of them had three or more pain conditions recorded, and the mean number of co-morbidities was 3.00.

Depression and anxiety were prevalent amongst long-term users and the disorders were present in 50.02% and 22.13% of the users, respectively. This suggested that long-term morbidities and mental health disorders were common health issues amongst the users and particularly amongst users of prolonged strong opioid use.

4.6.2 Characteristics of strong opioid users

4.6.2.1 Age and gender

The observed gender and age difference in the characteristics of strong opioid users could be explained by the prevalence of non-cancer pain. As the results confirmed, females and a progressive age were more likely to suffer from multiple pain conditions. Studies have indicated that age is generally associated with changes in the structure and function of the nervous system such as that of the nociception processing mechanism, which may result in a greater pain sensitivity, reduced pain tolerance, and lengthy recovery time from pain, which may, in turn, lead to the need for on-going pain management [297-299].

Indeed, this may also be the case in females, as implied by a number of researchers. For example, Riley L et al. (1998) conducted a meta-analysis to quantitatively compare pain intensity in females and males [300]. He found higher mean pain intensity, which ranged from 0.16 and 1.18 sd, and lower mean pain tolerance in females in the study than males. Moreover, in a prospective cohort study, Cepeda MS et al. (2003) followed a sample of non-cancer pain patients who had undergone ambulatory care to determine sex differences in pain perception, morphine consumption, and differences in analgesic responses [301].

Baseline pain intensity was found to be slightly greater in females: 8.0±1.7 for women; 7.6±1.7 for men, on a numerical pain rating scale, NRS (0=no pain, 10=worse pain). Moreover,

following the receipt of analgesics and upon the consumption of morphine, females were found to require 30% greater morphine doses to attain similar pain intensity reductions as males with equivalent to or less than a score of 4 in NRS.

In line with this, a few studies have indicated that females tended to report longer durations of pain and a more anatomically diffused pain compared to their male counterparts [302, 303].

4.6.2.2 Pain presentation

Noticeably strong opioid users had a range of clinical pain disorders diagnosed. In particular, many of the users had clinical pain presentation with definitive diagnosis such as back pain and osteoarthritis, whereas others had a less definitive diagnosis such as shoulder pain and neck pain.

For the frequent conditions of low back pain and osteoarthritis, although randomized controlled trials have shown pain reduction and moderate improvements in function with opioid use over short-term periods in highly-selected patient groups, continued long-term efficacy has only been assessed in few high-quality trials, and the use of chronic opioids in the respective conditions has remained inconclusive. For instance, a large systematic review by Martell and colleagues (2007) included 15 randomized controlled trials that assessed the efficacy of opioids in back pain of up to 3 months. Although reduction in pain score from baseline was observed in some of the trials for up to 16 weeks, in 4 trials, pain relief with opioids was similar to placebo, and efficacy beyond 16-weeks was not sustained [150]. In addition, improved function was not proved, and the author indicated a significant prevalence of substance-use disorder amongst the study population of up to one quarter of opioid recipients.

Similarly, Schofferman J et al. (1999) included 33 patients with chronic low back pain in a two phase trial, which initially involved a 6-12 week period of opioid use followed by an open-label follow-up trial of up to a year [304]. Improvement in pain and function from baseline was reported, and the mean pain score was found to reduce from a mean of 8.45 to 4.90 in numerical rating scale at the end of the 12 weeks.

However, as with any typical RCT participants, in Schofferman's study the patient selection criteria were highly constrained, and patients with structural pathology, psychiatric disorders, older ages, serious morbidities and histories of aberrant behaviour were excluded. This suggests that the results from the trial, even (favourable) at short-term use, are a reflection of the effect of the drug on the included types of patients, and ambivalent in a more heterogeneous population such as the patients in the current study [304].

Furthermore, recent reviews of RCTs have compared common non-opioids such as NSAIDs and antidepressants with opioids in chronic low back pain and have also reported less encouraging conclusions. Roelofs PD et al. (2008) included 65 trials, of which 28 were of high quality, and concluded that compared with placebo, NSAID showed minimal short-term efficacy in chronic low back pain but it had no greater efficacy compared with paracetamol, opioids and muscle relaxants [305]. In a different Cochrane review, Chaparro LE et al. (2013) reviewed 15 trials in which one of them directly compared opioids with NSAIDs in chronic low back pain, and the author reported that the evidence was of very low quality to suggest differences in analgesia [130]. The review further identified two trials that evaluated the efficacy of opioids versus antidepressants and concluded that there were no differences in pain relief and function between the two drug classes in chronic low back pain.

Comparably, in osteoarthritis, results from large reviews of RCTs concluded short-term reduction in pain intensity and minimal benefit on function relative to placebo [306]. Most importantly, it is worth stating that the average duration of trials was 13-18 weeks and, like the back-pain trials, many trials in the review precluded participation of patients with serious physical and psychiatric disorders, which again questions the applicability of the results to patients in real-world clinical settings.

4.6.2.3 Physical and psychological co-morbidities

Multi-morbidities that included psychological health disorders were found to be common amongst strong opioid users, and may reflect a multitude of clinical needs and competing demands of patients prescribed strong opioids. This may also suggest that further medical services and psychological counselling may be required. However, given that the average primary care consultation is estimated to cover 2.5 health conditions in 11.9 minutes, this may pose a clinical management challenge for the care of strong opioid users with multiple conditions [307]. In a different light, research has shown that there may be significant differences in the outcomes of opioid therapy in patients with non-cancer pain and with additional chronic medical morbidities compared to pain patients without comorbidities.

Ashworth J et al. (2013) assessed self-reported functional outcomes in patients with low back pain receiving opioids compared to those who were not during 6-months follow-up [162]. Patients prescribed opioids were found to have significantly greater comorbidities than those with no opioid prescribed, and after a 6-month follow-up period opioid, users had greater mean pain intensity ($p<0.001$), greater reported disability ($p<0.001$) and were more likely to report depression and anxiety ($p<0.001$), reduced self-reported efficacy ($p<0.001$) and reduced tendency of coping ($p<0.001$).

Equally, in a placebo-controlled trial Jamison RN et al. (2013) examined opioid therapy outcomes compared to placebo in patients with chronic low back pain (>6 months) who had high levels of depression and anxiety (negative affect) [308]. The result showed that patients with high levels of negative affect had more pain, had 40% more opioid analgesia, disability and were more likely to withdraw from treatment compared to their counterparts of chronic low back pain patients with low levels of negative effects. The author of the study suggested that the medical complexities of patients treated with opioids may potentially interact with their pain, its response, and may also affect treatment outcomes.

Indeed, further studies in the form of prospective surveys have demonstrated that depression promotes prolonged pain but, similarly, the existence of long-term pain can foster the development of depression, and that this bi-directional relationship may attenuate prolonged analgesic use [309]. Interestingly, Lin EHB et al. (2003), in a randomized controlled trial, were able to demonstrate that the management of depression through supervised medical psychotherapy in a highly specialised clinical setting was able to equivalently improve pain intensity and physical functioning in a study sample diagnosed with arthritis [310].

4.6.3 Traits of long-term users

It was clear from the current study that non-cancer pain patients who used strong opioids long-term during the study period were further characterized by a number of pain and co-morbid illnesses, suggestive of constellations of physical problems within this population. More importantly, conditions that were commonly reported, such as cardiovascular, respiratory and renal diseases, are also known to be in conflict with opioid therapy [181, 191, 311-313].

Opioids have a direct effect on the respiratory and cardiovascular system and can intensify the severity of pre-existing conditions related to the organ systems, and can attenuate fatal consequences [191, 311]. Accordingly, consensus guidance recommends the avoidance of long-term opioid use in chronic pulmonary disease (except in terminal stages) and product information guidance advises the adoption of strict cautionary use in cardiac disorders [314, 315]. Further, special care is urged in patients with chronic kidney disease (CKD) and liver disease due to the risk of an accumulation of opioid metabolites (with continued use) which results in a greater risk of toxicity [316].

The clinical traits of the users observed in the current study is consistent with prior international publications, particularly in the US where studies have shown an increased likelihood of patients with chronic non-cancer pain and comorbid chronic conditions to receive opioid therapy [281, 283]. Sullivan MD et al. (2013) have termed this phenomenon "adverse selection", where high-risk patients are likely to receive the high-risk drug class [317]. The concept of adverse selection was originally discerned from two large pharmacoepidemiological studies conducted to investigate the trend in opioid therapy in the last decade [318, 319]. The Trend and Risks of Opioid Use for Pain (TROUP) studies used two large representative US healthcare insurance claims databases, one commercial (HealthCore) and one state-based (Arkansas Medicaid), to assess diagnostic disorders and opioid treatment in two dissimilar populations from 2000 through to 2005.

The studies reported a linear growth in the prevalence of chronic non-cancer pain patients using opioids in both the commercially insured and publicly insured databases over the 6-year study time. Part of the increase was attributed to a rise in the long-term supply of opioids beyond 90 days per year and a rise in the use of more potent opioids. Patients with physical and

psychological morbidities were over-represented and long-term opioid use was found to increase rapidly amongst this subgroup, suggesting that long-term opioid therapy was progressively augmented in high-risk patients [318, 319].

The presence of multiple long-term comorbidities, either inclusive or exclusive of pain, poses an additional clinical challenge. This is because in the UK, management of long-term conditions are based on clinical guidelines that are focused on individual single conditions and evidently, it has been argued, that this limits the applicability of the recommendations to the holistic management of multiple co-existing chronic conditions and the use of multiple guidelines could in essence increase unwarranted drug-interactions, drug-disease interactions and drug-food interactions [320]. Boyd CM et al. (2005) demonstrated this through a narrative description of the clinical management of elderly patients with several co-existing chronic conditions such as osteoporosis, diabetes, hypertension, COPD and osteoarthritis [321]. He illustrated that for patients to be compliant with all the management recommendations from relevant guidelines; patients' therapeutic and non-therapeutic treatment would consist of 12 pharmacological and 14 non-pharmacological regimens.

In light of this, recently the National Institute for Health and Care Excellence (NICE) published recommendations on the assessment and management of patients with multimorbidities [50]. However, given the dearth of research in this area of care, the recommendation remains markedly generic.

4.6.4 Strengths and limitations

This is the first study, to the best of our knowledge, to use primary care representative data to identify, describe and quantify pain conditions and QOF related long-term morbidities among

non-cancer pain patients prescribed strong opioids, particularly in patients prescribed long-term strong opioid therapy. However, it has not been possible to point out the specific pain condition(s) for which the patients were prescribed the strong opioid treatment for due to the multiple pain conditions recorded.

Furthermore, the study used Quality Outcomes Framework clinical areas to pragmatically identify long-term morbidities of the study population. The advantage of the approach is that the lists of QOF morbidities are likely to have been reliably and consistently recorded in the GPs database, and hence in CPRD. However, as QOF only encompasses most common long-term conditions in primary care, there may have been other long-term co-morbidities that were not identified in the study sample.

Similarly, despite the use of a comprehensive list for read codes for a wide range of pain conditions using CPRD medical dictionary system, it is likely that diagnostic pain conditions for some users were not identified. Nevertheless, the approach used was able to trace conditions in 82.13% of the study population.

4.6.5 Conclusions

The results suggest that the characteristics of patients who received strong opioids and for long periods are not necessarily reflective of the population included in clinical trials. Conversely, given that the provision of adequate pain relief is considered an important standard of care, the findings of the clinical traits of strong opioid users identifies patients who may need closer attention in practice. Moreover, further investigations are needed to establish patient-level prescribing patterns of the users in detail in order to further assess the appropriateness of the treatment.

Chapter 5 Patterns of long-term versus short-term strong opioid prescribing in non-cancer pain patients and factors influencing long-term use

5.1 Introduction

The two previous chapters have focused on determining changes in the prevalence and incidence of strong opioid users over time, and explored the demographic and co- existing morbidities of the users, with an attentive examination of patients on long-term therapy.

However, when examining drug utilisation, it is ideal to measure and quantify drug consumption at patient-level. It is generally known that an effective drug therapy requires that the drug to be used at an appropriate dose-level and for an appropriate length of time. However, for opioids, the length of use and dose carry potential risks, (adverse effects, tolerance, problematic drug use), which makes it a relevant issue with clinical implications [174, 322, 323].

It is perhaps for such reason that it becomes acutely relevant to study patients' dose use over time. One way to capture this is to study the prescribed daily oral morphine equivalent dose (OMED), and presuming that the information on the prescribed dose can be deduced over time, it becomes possible to determine the length of dose treatment.

Morphine equivalent metrics were developed by the WHO collaborating Centre for Drug Statistics Methodology (WHOCC) and were originally used in cancer pain treatment to guide clinicians on the appropriate dose switching and conversions between different opioids relative to morphine (morphine being the first line drug of choice in many instances) [324]. The use of OMED has subsequently become a universal unit of measurement for dose conversions between different opioids that are prescribed for the purpose of managing non-cancer pain [325-327].

National and international guidelines governing the use of opioids for patients with chronic non-cancer pain have relied on the OMED concept as a tool for regulating the safe prescribing of opioids in practice. Despite marginal differences between international guidelines, the upper opioid dose limits in chronic non-cancer pain have been recommended as a maximum daily dose of 120 mg in the British guideline, 100 mg/day in the Australian recommendation and below 90 mg in the recently updated American and Canadian guidelines [47, 328-330].

Such dose limits stem from the knowledge that, despite the graded response that opioids elicit at low doses, the response at higher doses eventually levels off, and patients may only experience minimal analgesia. Moreover, continued use of the drugs at higher doses may become futile, and it has been shown that the use of high doses over prolonged periods is associated with opioid use disorders and risks of toxicity [185, 195, 331]. Furthermore, increased effectiveness of opioid use exceeding 100-120mg/day has not been confirmed in clinical trials and as such, there is little evidence and confidence to support high dose use long-term [209].

A pattern that has also raised safety concerns is the co-prescribing of benzodiazepines. This carries a level of risk, which includes unintentional overdose when combined with opioids for prolonged usage, and it is a use that has been cautioned for in most recommendations. However, international expert consensus has varied from deeming the combination as contraindicatory to recommending a cautionary use only, with enhanced monitoring, to ensure mitigations of potential drug-combined risks [288, 330, 332, 333].

Besides dose consumptions; international researches have also reported on a number of other factors that may predict non-cancer pain patients' long-term opioid use. Some of the studies have used short-term use as a comparative control in multivariate analysis and found that users

who were unemployed, had low incomes, lower education levels, and were on disability pension had a significantly greater probability to be on long-term opioid use [282, 334-336]. Most of the studies have been conducted outside the UK, which makes it difficult to unconditionally generalise the findings to the national population, and little remains to be known about the socio-economic and clinical variables associated with long-term opioid prescribing in non-cancer pain patients in the UK.

Likewise, to the best of our knowledge, no prior UK studies have explored morphine equivalent dose use in non-cancer pain patients prescribed strong opioids long-term in primary care. Gaining such knowledge would be a useful and a crucial trajectory in assessing patients' therapeutic treatment, but also facilitate a better understanding of the interplay between patients' social circumstances, morbidities, demographics and opioid use in clinical practice.

5.2 Aims and objectives

This study aimed to examine treatment patterns, including the distribution of oral morphine equivalent daily dose and duration of drug treatment amongst long-term users, using short-term users as reference. A secondary aim was to deduce covariates linked to long-term strong opioid use.

The objectives for this chapter were to:

1. Examine frequency of strong opioid prescribing in terms of average number of prescriptions issued per user per year among long-term users versus short-term users.
2. Examine average oral morphine equivalent daily dose (OMED) and average durations (in number of days) of strong opioid supply to long-term users versus short-term users per year.

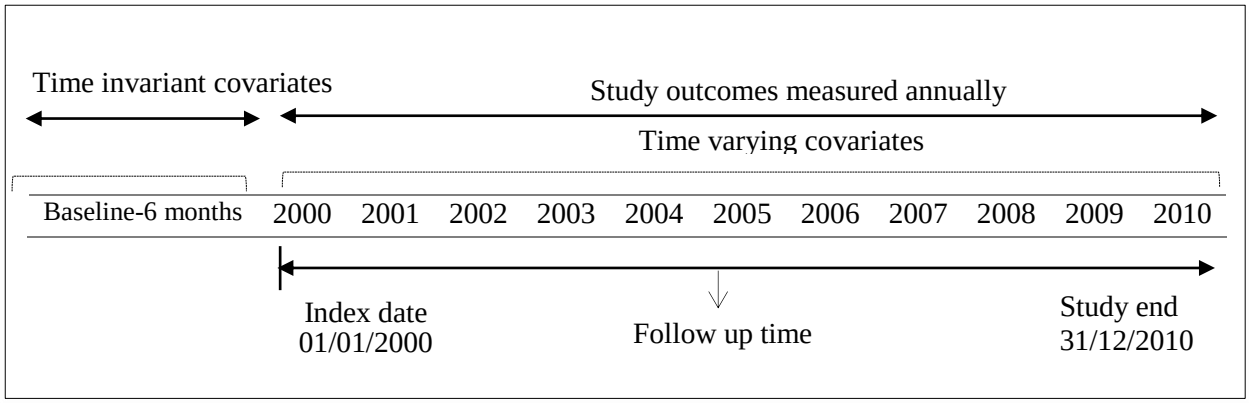
3. Explore co-prescriptions issued, particularly of medications that may have an adverse interaction with opioids such as benzodiazepine, anxiolytics, antipsychotics, anticonvulsants and antidepressants per person per year, and the extent of co-prescriptions with weak opioids and non-opioids (e.g. NSAIDs, Paracetamol).
4. Identify time-varying and time-invariant factors linked to long-term strong opioid use.

5.3 Method

5.3.1 Study design

This study adopted a retrospective longitudinal study design to examine non-cancer pain patients' patterns of strong opioids use in each year of the follow-up. Time-varying and time-invariant covariates were measured and entered in a multivariate analysis to determine their link to long-term strong opioid use per year (Figure 5-1).

Figure 5-1 Outline of the longitudinal study design



5.3.2 Study subjects

Adult (≥18 years) non-cancer pain patients defined, extracted and analysed in chapter 3 and chapter 4 made up the study population for this study. This comprised 135,941 adult patients in the Clinical Practice Research Datalink who had one or more prescriptions of strong opioids (fentanyl, buprenorphine, oxycodone, morphine) between January 1st 2000 and 31st December 2010.

Strong opioid users in the current study were re-defined and sub-grouped according to their calculated length of strong opioid supply in each year of follow-up as: strictly short-term users (≤90 days in each year of use) and long-term users (>90 days in each year of use) in the years of strong opioid use. Hence the study excluded users who had both short-term and long-term

days' supply (episodic users: 16.56% of all strong opioid users) to allow an analytical comparison of outcomes between long-term and short-term users.

5.3.3 Study outcome measures

The primary prescribing outcomes for this study were: 1) number of prescriptions issued per user per year; 2) daily dose use per user per year; and 3) days' supply per user per year. The outcomes were calculated separately for the two user groups and measured during the follow-up time.

The follow-up period was defined as the date of the first recorded prescription (i.e. index-date) on or after 1st of January 2000 till the end date. The end date was the end of the study period on 31st December, or the date of patient death, date of patient transfer out of general practice, or the last date of data collection, whichever occurred first.

5.3.3.1 Number of strong opioid prescriptions per user per year

The overall number of prescriptions was repeatedly calculated in each calendar year for each patient from the index date and throughout the follow up time. The average number of prescriptions per user per year was sequentially determined by dividing the total number of prescriptions received in a year by total number of users in the same year.

5.3.3.2 Oral morphine equivalent daily dose per user per year

The annual daily dose of strong opioids was calculated in accordance with the method described by Von Korff M et al. (2008) [137]. This was carried out by initially deriving the total morphine equivalent dose and subsequently estimating the daily dose.

5.3.3.2.1 Oral morphine equivalent dose

The dose of each prescription issued to each user in each calendar year was calculated by multiplying prescription quantity by the strength of the prescription medication in milligrams. The dose or quantity-strength result was subsequently multiplied by an equianalgesic conversion ratio for oral morphine equivalent to estimate the oral morphine equivalent dose for the prescription. The conversion ratio refers to the relative analgesic potency that is equivalent to 10mg of parenteral morphine sulphate. This was used to standardise the dose of the different opioids examined relative to morphine (Table 5-1).

Table 5-1 Morphine equivalent equianalgesic conversion ratios

Opioid	**Morphine equianalgesic ratio**
Fentanyl Transdermal	100
Fentanyl SL	50
Oxycodone	1.5
Buprenorphine Transdermal	110
Buprenorphine Sublingual	50

Note: Equianalgesic ratio: potency of respective opioid/opioid formulations compared with oral morphine. **Source**: Svendsen K et al. (2011) [337].

5.3.3.2.2 Oral morphine equivalent daily dose

The total morphine equivalent dose was calculated by adding all the morphine equivalent doses for each prescription for each patient in each calendar year. The total morphine equivalent dose was then divided by the total days' supply to derive an average oral morphine equivalent daily dose.

a) Oral morphine equivalent dose = Quantity x Strength (mg) x Equianalgesic ratio

b) Oral morphine equivalent daily dose = $\frac{\text{Oral morphine equivalent dose}}{\text{Days' supply}}$

5.3.3.3 Number of days' supply per user per year

The length of each prescription in number of days was calculated as described in chapter 3, section 3.3.3.2 (page 84). The mean number of days' of supply per user per year was calculated by dividing the total number of days' supply by the number of users in the same year.

5.3.4 Study covariates

Independent patient-level variables that have been shown in international and national studies to be associated with opioid prescribing, but have not necessarily been examined in the prescribing of strong opioids, were examined in this study. This included demographic, lifestyle, long-term health conditions, polypharmacy and primary healthcare use variables [159, 274, 281, 338-344] (Table 5-3). Demographic variables consisted of age, gender, patients' practice region and Townsend deprivation score. Lifestyle variables encompassed smoking and body mass index (BMI). Long-term illnesses consisted of pain-related conditions and general comorbidities, including psychiatric disorders, and primary health service use, including the number of general practice consultations (Table 5-3).

Since longitudinal studies are likely to produce time-varying and time-invariant variables, all patient-level variables in this study were measured as either time-varying or time-invariant variables [226] (Table 5-2). The choice of which variables were to be measured at a fixed time frame and which variables were measured repeatedly over time was based on the nature of the variables and whether the variables would be consistently available over the study period.

Table 5-2 Definition of study covariates

Covariates	Variable	Definition in the study	Time frame measured
Age	Nominal	Time-invariant	At index date
Gender	Binary	Time-invariant	At index date

(Continued) Table 5-2 Definition of study covariates

Covariates	Variable	Definition in the study	Time frame measured
Region	Nominal	Time-invariant	At index date
Townsend score	Ordinal	Time-invariant	At index date
Pain conditions	Binary	Time-invariant	Up to 6 months <index date
Comorbidities	Binary	Time-invariant	Up to 6 months <index date
Smoking	Nominal	Time-invariant	At index date
Co-prescriptions	Binary	Time-varying	Annually during follow-up
GP consultations	Nominal	Time-varying	Annually during follow-up

5.3.4.1 Time-invariant covariates

5.3.4.1.1 Socio-demographic and clinical variables

Patients' age, gender, practice region and Townsend deprivation score were defined as time-invariant variables and measured at index date (first prescription date) (Table 5-3). Information on patients' smoking status (non-smoker, current smoker and ex-smoker) and BMI was additionally measured at index date. These were extracted from CPRDs' clinical and additional files using information recorded in the files as medical and enttype codes of smoking and BMI.

The proportion of patients who had pain diagnoses, long-term morbidities defined by the Quality and Outcomes Framework (QOF, version 27) and psychiatric disorders were determined up to 6 months prior to users' first prescription use, i.e. before the index date (Table 5-3). The conditions were identified in users' clinical, consultation and referral files through the use of medical codes, which were traced and obtained from CPRDs' medical dictionary as described in chapter 4. The QOF morbidities were categorised into cardiovascular morbidities, endocrine diseases, respiratory diseases, central nervous system-related morbidities, musculoskeletal and other disorders for analysis (Appendix 12). Medical information of the users that was recorded up to 6 months before the index date, within users' registration date,

practice-up-to-research standard date and before their practice transfer out of date were included in the analysis.

Table 5-3 Factors that are potential influencers of strong opioid prescribing to be investigated

Factor	Definition	Hypothesis
Age	Age was tested as a categorical variable (1=<50 years, 2=50-64 years, 3=65-74 years, 4=≥75 years)	Peak age of opioid initiation and long-term use has been reported in ≥50 years and in elderly patients (>65years) [274, 339, 345-347].
Gender	Gender was set as a binary variable (0=Male, 1=Female).	Whenever differences were found, long-term opioid use was more common in females [335, 338, 339, 348].
Region of residence	Practice regions were examined as a categorical variable (1=North East, 2=North West, 3=Yorkshire & Humber, 4=East Midlands, 5=West Midlands, 6=East of England, 7=South West, 8=South Central, 9=London, 10=South East).	Opioid prescriptions issued have been shown to be greater in North East of England [349]. Studies comparing long-term opioid prescribing in relation to English regions (particularly of strong opioids and in non-cancer pain) have not been conducted.
Socioeconomic status	Townsend deprivation index was used as a marker for socioeconomic status. Socioeconomic status was defined as 5 quintiles of Townsend score with 1=least deprived and 5=most deprived.	Low-income patients tended to report more chronic pain conditions and be on long-term opioid treatment [213, 215, 334, 350].
Comorbidities	Co-morbidities were addressed as binary variables as either having morbidity (=1) or not (=0). Long-term morbidities defined by QOF (business rule 27) were used [246].	Higher burden of medical comorbidity have been reported in patients on prolonged opioid therapy [280, 343, 351].
Smoking	Smoking status of patients was defined as a categorical variable with 1=non-smoker, 2=smoker and 3=ex-smoker.	Smoking and nicotine dependence have been linked to long-term opioid therapy through a possible effect on pain processing [280, 343, 351, 352].
Obesity	Obesity was classified as a binary variable (0=BMI≤30kg/m^2, 1=BMI>30kg/m^2).	Few studies demonstrate link between obesity and prolonged opioid use. Obesity's co-existence with chronic pain or suggestive effects of opioids on glycaemic control have been proposed as possible reasons [281, 353, 354].

5.3.4.2 Time-varying variables

5.3.4.2.1 Co-prescriptions

As a reflection of patient psychiatric comorbidity and therapeutic pain management, we assessed patients who were exposed to prescription medications related to such indications. This included antidepressants, benzodiazepines and non-benzodiazepine sedative-hypnotics, antipsychotics, as well as non-steroidal anti-inflammatory drugs, paracetamol, anticonvulsants, weak opioids and tramadol prescriptions. These were classified as time-varying dichotomous variables and their prescribing was identified for each user in each year during follow up. A dummy variable was created for each of the drugs where 1 indicated users who had one or more of the specific medications co-prescribed in the same year as strong opioid prescriptions during follow-up, and 0 if not.

5.3.4.2.2 Data management of co-prescriptions

5.3.4.2.2.1 Weak opioids, NSAIDs, paracetamol and tramadol

Non-opioid analgesics (NSAIDs, paracetamol and tramadol), weak opioids and tramadol drug prescriptions issued to strong opioid users during the follow-up period were identified in the therapy file by applying related product codes that were identified from the CPRDs' product dictionary (Appendix 15).

5.3.4.2.2.2 Psychoactive medication

The study focused on 4 major classes of psychoactive medications; benzodiazepines, non-benzodiazepines, antidepressants and antipsychotics (Appendix 16). Benzodiazepines and non-benzodiazepine based sedative-hypnotics included Amobarbital sodium, Butabarbital, Chlordiazepoxide, Chloral hydrate, Clomethiazole, Diazepam, Flurazepam hydrochloride,

Hydroxyzine, Lorazepam, Lormetazepam, Meprobamate, Nitrazepam, Oxazepam, Secobarbital, Temazepam, Zaleplon and Zolpidem tartrate [121].

Antipsychotic drugs that were studied included: Amisulpride, Aripiprazole, Chlorpromazine hydrochloride, Clozapine, Flupentixol dihydrochloride, Haloperidol, Olanzapine, Paliperidone, Pericyazine, Perphenazine, Pimozide, Prochlorperazine maleate, Promazine Hydrochloride, Quetiapine, Risperidone, Sulpiride, Trifluperazine hydrochloride and Zuclopenthixol dihydrochloride [121]. In the same manner as weak opioids and non-opioids, the drugs were identified from CPRD product dictionary browser, and related product codes were applied to users' therapy files to identify individual users who were prescribed the drugs during follow-up (Appendix 16). Injection formulations and benzodiazepines licensed for pre-operative and anaesthesiology use were excluded.

5.3.4.2.2.3 Drugs with dual indications

Many antidepressants are indicated and used to manage psychiatric disorders, and for the management of chronic pain such as neuropathy [121]. In this study it was not feasible to distinguish the indication of the antidepressants prescribed due to the presence of multiple diagnostic codes in users' medical records. Antidepressants that were examined included tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and other antidepressants (Appendix 16).

Similarly, anticonvulsants are known to have dual clinical indications, and can be used in the management of epilepsy and for certain chronic pain conditions (e.g. migraine, neuropathic pain) [121]. In order to ensure that anticonvulsant co-prescriptions were analysed as analgesics

the medications were examined in users' who did not have diagnostic Read codes for epilepsy at index date.

The total number of days' supply of co-prescribed medications was calculated for each user in each calendar year by dividing co-prescriptions' quantity by prescriptions' numerical daily dose (NDD). Missing NDDs were imputed using the median numerical daily dose (not mean due to the non-normality of the NDD dataset of similar drug prescriptions, i.e. product codes in the dataset) of patients with similar age and gender and with known NDD values (the majority of the co-prescribed drugs classes are often recommended on the basis of the two parameters) [121]. Summary statistics were used for diagnostic measure and to ensure data consistency before and after imputation (Appendix 17).

5.3.4.2.3 General practice visits

Consultation records of strong opioid users were accessed through CPRDs' consultation file. The total number of GP visits was calculated for each user in each year during follow-up from the index date, and dummy categorical variables were created where 1=1-3visits/year, 2=4-7 visits/year, 3=8-11 visits/year and 4=≥12 visits/year.

5.4 Data analysis

5.4.1 Analysis of user-groups and outcome measures

Descriptive statistics were used to report on patient-level characteristics of short-term and long-term users and this was presented as mean±standard deviation, crude numbers and percentages. Differences in socio-demographic and clinical data between the two user-groups were analysed using Pearson's chi-squared test for categorical variables and t-test for independent normally distributed continuous variables. Tests with *p*-value of ≤0.05 were considered statistically significant.

Descriptive statistics were also used to report the outcome measures in the two user-groups in terms of average prescriptions issued per user, average oral morphine equivalent daily dose and average number of days' supply per user per year together with their respective standard deviations. Joinpoint regression analysis was computed as described in chapter 3 (page 87) to evaluate statistically significant changes in the trend of each of the outcome measures over time [251, 252]. Annual percent change (APC) for each trend was computed using year as the independent predictor variable and a *p*-value of ≤0.05 was considered significant.

Data on oral morphine equivalent daily doses of strong opioids were further analysed to estimate the proportions of long-term and short-term users prescribed high doses per year. High daily dose was defined as a use of greater than 120mg oral morphine equivalent daily dose according to recommendations [47].

5.4.2 Multivariate analysis of covariates linked to long-term use

Multivariate analysis was used to determine covariates that were linked to the odds of long-term strong opioid use during follow up. Type of user was entered in the multivariate analysis

as the dependent variable and as a binary categorical variable with 1=long-term user in each year, 0=short-term user in each year. Since the dependent variable was a repeat measure per year, consequently standard regression methods such as linear and logistic regression were inappropriate to be used as the preferred method of multivariate analysis. This is mainly because of the occurrence of correlation between the measures in each year, which thus violates the non-independence assumption of the standard regression method.

The influence of covariates on the dependent measure was assessed using the generalized estimating equation. Essentially GEE, which is an extension of generalized linear regression, accounts for correlations in the analysis of longitudinal data to achieve efficient and accurate parameter estimations without making specific distributional assumptions [227, 355] (Appendix 18). Age, gender, region, Townsend score, type of pain diagnoses and long-term comorbidities were included in the model as time invariant covariates and the prescribing of psychoactive medications, weak-opioids and non-opioid analgesics and annual GP consultations were included as time-varying (and as binary and nominal) covariates. The dependent dichotomous variable (type of user) was described as a function of the covariates using GEE model with binomial distribution, a logit link function (to specify logistic regression analysis of the dichotomous dependent variable) and an independent working correlation structure (which implied that the correlations between repeated observations of the response variable was assumed to be independent, Appendix 19).

Unadjusted or crude odds ratios were initially estimated for each covariate to examine individual relationships with the outcome measure before regressing the covariates in an adjusted analysis. This was followed by the development of two different adjusted models using GEE: in Model A, all covariates that were time-independent from baseline were initially

included in the regression analysis and subsequently, in Model B, a second GEE model was used to incorporate all time-varying variables, measured at different follow-up time-points. Thus, the three statistical modelling approaches made it possible to assess the influence of the baseline (unadjusted model), time-independent factors (Model A) and time-dependent factors (Model B) on the prediction of strong opioid long-term use.

Results from the GEE models were presented as unadjusted and adjusted odds ratio (aOR) with 95% confidence interval (95%CI). A *p*-value of ≤0.05 was considered statistically significant. The analysis was conducted using STATA, version 14.0 (Stata Corporation, College Station, TX, USA) and Joinpoint Regression Program, version 4.5.0.1

5.5 Results

5.5.1 Characteristics of study user-groups

Of the baseline population (n=135,941) of non-cancer pain patients prescribed strong opioids between 2000-2010; 63.80% (n=86,725) were short-term users in each year of follow-up and 19.64% (n=26,703) were strictly long-term users per year. The mean follow-up duration of long-term users was 4.48±3.02 years (range: 1-11 years), and for short-term users this was 1.55±1.10 years (range: 1-11 years).

Although the mean age of long-term users (65.31±17.07 years, mode: 77; range: 18–107 years) was slightly lower than short-term users (67.45±18.39 years, mode: 77; range: 18–107 years), the largest proportions of long-term users were in the age group of 66-80 years (30.73%). Most long-term and short-term users were females who made up almost two-thirds of all users in each of the two-groups (64.99% and 62.59%, respectively). There were greater proportions of long-term users who were smokers (27.18%) than in the short-term user group (24.96%) (Table 5-4).

Table 5-4 shows a comparison of the most common pain conditions between the two user groups. Back pain and osteoarthritis were common pain complaints up to 6 months before the index date, and were more prevalent amongst long-term strong opioid users (19.75%, 6.18%, respectively) than short-term users (17.28%, 4.75%, respectively). In contrast, abdominal pain (7.94%, versus 5.35%) and shoulder pain (4.35% versus 3.71%) were more frequent in short-term users. Moreover, a slightly higher proportion of short-term users had cardiovascular and respiratory related QOF comorbidities before the first prescription use than long-term users.

Table 5-4 Comparison of characteristics of long-term and short-term strong opioid users

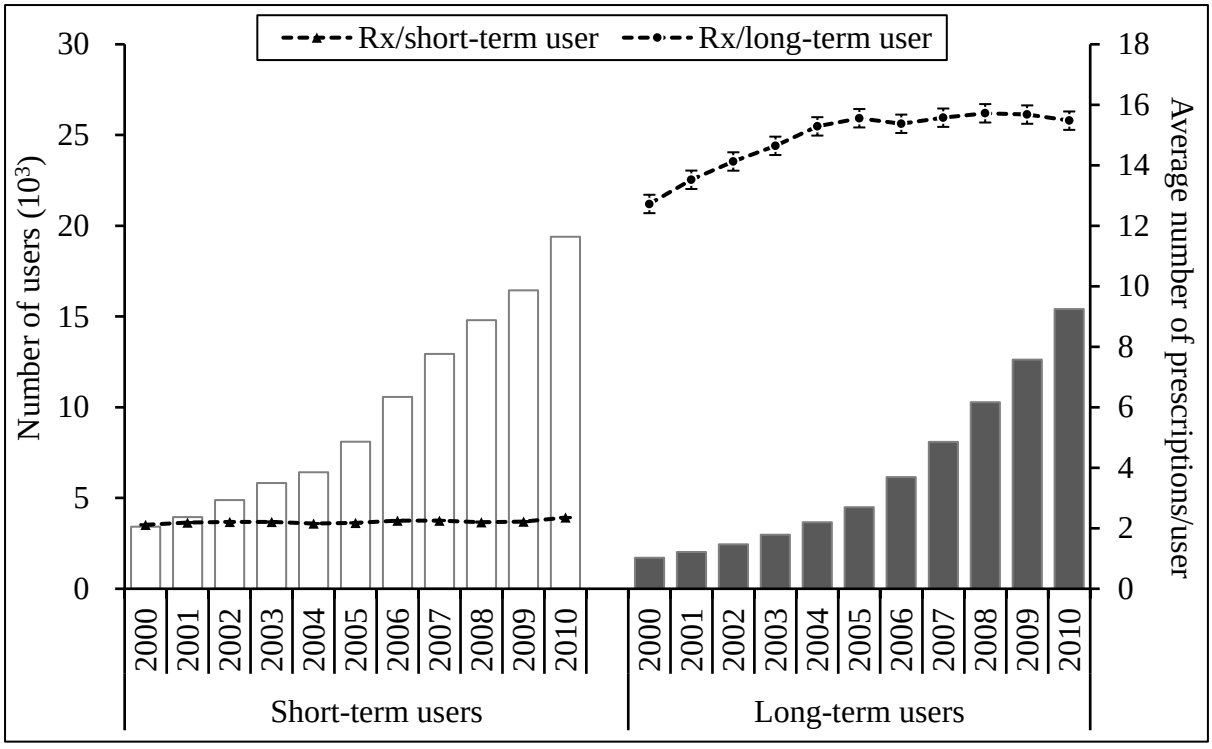
	Short-term users	**Long-term users**	**Test (df)**	***P*-value**
Mean age±SD	67.45±18.39	65.31±17.07	t(113,426)=16.92	<0.001
Rank of age				
≤40 years	8,887 (10.25%)	2,508 (9.39%)		
41-50 years	8,773 (10.12%)	3,356 (12.57%)		
51-65 years	18,095 (20.86%)	6,753 (25.29%)		
66-80 years	26,215 (30.23%)	8,206 (30.73%)		
≥81 years	24,755 (28.54%)	5,880 (22.02%)	$X^2(4)= 635.58$	<0.001
Gender				
Male	32,443 (37.41%)	9,348 (35.01%)		
Female	54,278 (62.59%)	17,355 (64.99%)	$X^2(1)= 50.68$	<0.001
Townsend score				
1 least deprived	19,474 (22.45%)	5,634 (21.10%)		
2	21,421 (24.70%)	6,237 (23.36%)		
3	18,746 (21.62%)	5,818 (21.79%)		
4	16,935 (19.53%)	5,424 (20.31%)		
5 most deprived	10,149 (11.70%)	3,590 (13.44%)	$X^2(4)= 98.48$	<0.001
Smoking status				
Smoker	21,645 (24.96%)	7,259 (27.18%)		
Non-smoker	32,610 (37.60%)	10,197 (38.19%)		
Ex-smoker	32,470 (37.44%)	9,247 (34.63%)	$X^2(2)= 73.51$	<0.001
Pain diagnosis				
Back pain	14,988 (17.28%)	5,273 (19.75%)	$X^2(1)= 84.53$	<0.001
Abdominal pain	6,887 (7.94%)	1,428 (5.35%)	$X^2(1)= 202.15$	<0.001
Osteoarthritis	4,116 (4.75%)	1,651 (6.18%)	$X^2(1)= 87.34$	<0.001
Shoulder pain	3,776 (4.35%)	992 (3.71%)	$X^2(1)= 20.71$	<0.001
"Others"	18,588 (21.43%)	5,114 (19.15%)	$X^2(1)= 64.31$	<0.001
Comorbidities				
Cardiovascular	5,836 (6.73)	1,413 (5.29)	$X^2(1)= 70.55$	<0.001
Musculoskeletal	1,839 (2.12)	746 (2.79)	$X^2(1)= 41.55$	<0.001
Endocrine	2,011 (2.32)	672 (2.52)	$X^2(1)= 3.46$	0.06
Respiratory	2,676 (3.09)	724 (2.71)	$X^2(1)= 9.84$	0.002
CNS	2,007 (2.31)	602 (2.25)	$X^2(1)= 0.32$	0.57
"Others"	1,811 (2.09)	503 (1.88)	$X^2(1)= 4.27$	0.04
Psychiatric disorders				
Depression	1,208 (1.39%)	371 (1.39%)	$X^2(1)= 0.00$	0.97
Anxiety	930 (1.07%)	309 (1.16%)	$X^2(1)= 1.36$	0.24

Significance at $p \leq 0.05$

5.5.2 Prescribing frequency per year

On average, long-term users received 14.88±12.64 prescriptions per year during follow up. This was 7 times more prescriptions issued to long-term users than short-term users per year. Short-term users received an average of 2.23±2.14 prescriptions per year. While the average number of prescriptions issued to short-term users remained constant over time, the number of users prescribed the drugs short-term continued to increase by an annual percentage change of 19.72% (95%CI: 18.40, 21.10, p<0.001) from n=3,420 users in 2000 to n=19,397 in 2010 (Figure 5-2).

Figure 5-2 Number of users and average number of prescriptions/user stratified by user-group



Conversely, the average number of prescriptions received by long-term users increased annually by 1.86% (95%CI: 1.00, 2.70, p<0.001) from an average of 12.72±10.78 prescriptions in 2000 to 15.48±13.45 prescriptions per user in 2010 (Table 5-5). At the same time, the

number of users who received long-term treatment increased by 25.64% (95%CI: 24.10, 27.20, $p<0.001$) per year from n=1,712 users in 2000 to n=15,406 in 2010 (Figure 5-2).

Table 5-5 Average annual prescriptions per user and annual percent change per year

Study user-group	2000	2010	Years	APC (95%CI)
Short-term users	2.11±2.02	2.35±2.12	2000-2010	0.61 (0.20-1.00)*
Long-term users	12.72±10.78	15.48±13.45	2000-2010	1.86 (1.00-2.70)*

*Annual percent change (APC) with 95% confidence intervals statistically significant at $p\leq0.05$

5.5.3 Patterns of oral morphine equivalent daily dose and duration of drug supply

There were significant differences between the two user-groups with respect to the daily dose of strong opioids prescribed. Long-term users received almost twice the average oral morphine equivalent daily dose (OMED) compared to users on short-term therapy. Long-term users had an average annual OMED of 95.88±109.03 mg/day, whereas short-term users received an average of 54.80±54.55mg/day per year (Table 5-6).

Table 5-6 displays the trend in the average annual daily dose prescribed per user during the study period. In both user-groups the average OMED increased initially from 2000 to 2005 from 62.57±56.22mg/day to 67.67±56.29mg/day in the short-term user-group and from 98.69±110.56mg/day to 119.07±119.06mg/day amongst long-term users, respectively. The OMED levelled off thereafter, and at the end of the study the average daily dose in the short-term user group was 45.40±36.54mg per year, and 80.62±89.49mg per year in long-term users.

Meanwhile, the mean annual days' supply per user for long-term users continued to rise during the study period, reflecting prolonged treatment. The increase was by 0.79% (95%CI: 0.50,

1.10, $p<0.001$) annually from an average of 231.11±85.05 days in 2000 to 255.29±91.99 days per long-term user in 2010 (Table 5-6).

Table 5-6 Average annual oral morphine equivalent (OMED) dose per day per user and days' supply per user stratified by user group

Type of user						
Short-term users				**Long-term users**		
Year	**N (%)**	**Mean OMED/year, mg**	**Mean days' supply/year**	**N (%)**	**Mean OMED/year, mg**	**Mean days' supply/year**
2000	3,420 (3.94)	62.57 (56.22)	26.31 (21.38)	1,712 (6.41)	98.69 (110.56)	231.11 (85.05)
2001	3,949 (4.55)	65.14 (140.20)	25.98 (21.12)	2,033 (7.61)	101.89 (133.63)	238.24 (88.37)
2002	4,887 (5.64)	65.49 (55.95)	26.41 (21.69)	2,446 (9.16)	109.28 (158.79)	241.71 (89.97)
2003	5,826 (6.72)	68.83 (75.95)	25.66 (21.13)	2,972 (11.13)	112.87 (149.67)	244.97 (91.65)
2004	6,420 (7.40)	66.79 (55.45)	25.45 (20.61)	3,672 (13.75)	115.47 (129.24)	248.95 (89.23)
2005	8,102 (9.34)	67.67 (56.29)	25.60 (20.50)	4,497 (16.84)	119.07 (119.06)	249.50 (89.11)
2006	10,570 (12.19)	60.47 (51.35)	27.01 (21.32)	6,146 (23.02)	108.56 (109.33)	243.67 (90.59)
2007	12,940 (14.92)	53.09 (47.48)	27.23 (21.21)	8,090 (30.30)	99.57 (106.22)	247.76 (90.60)
2008	14,801 (17.07)	48.09 (39.86)	27.39 (21.08)	10,274 (38.48)	92.88 (101.23)	251.64 (90.00)
2009	16,444 (18.96)	46.38 (34.84)	28.13 (21.41)	12,619 (47.26)	86.48 (95.71)	253.42 (89.22)
2010	19,396 (22.36)	45.40 (36.54)	30.71 (22.72)	15,406 (57.69)	80.62 (89.49)	255.29 (91.99)
Total average/user/year		**54.80 (54.55)**	**27.57 (21.51)**		**95.88 (109.03)**	**249.81 (90.39)**

5.5.3.1 Patterns of high versus low dose oral morphine equivalent daily dose use

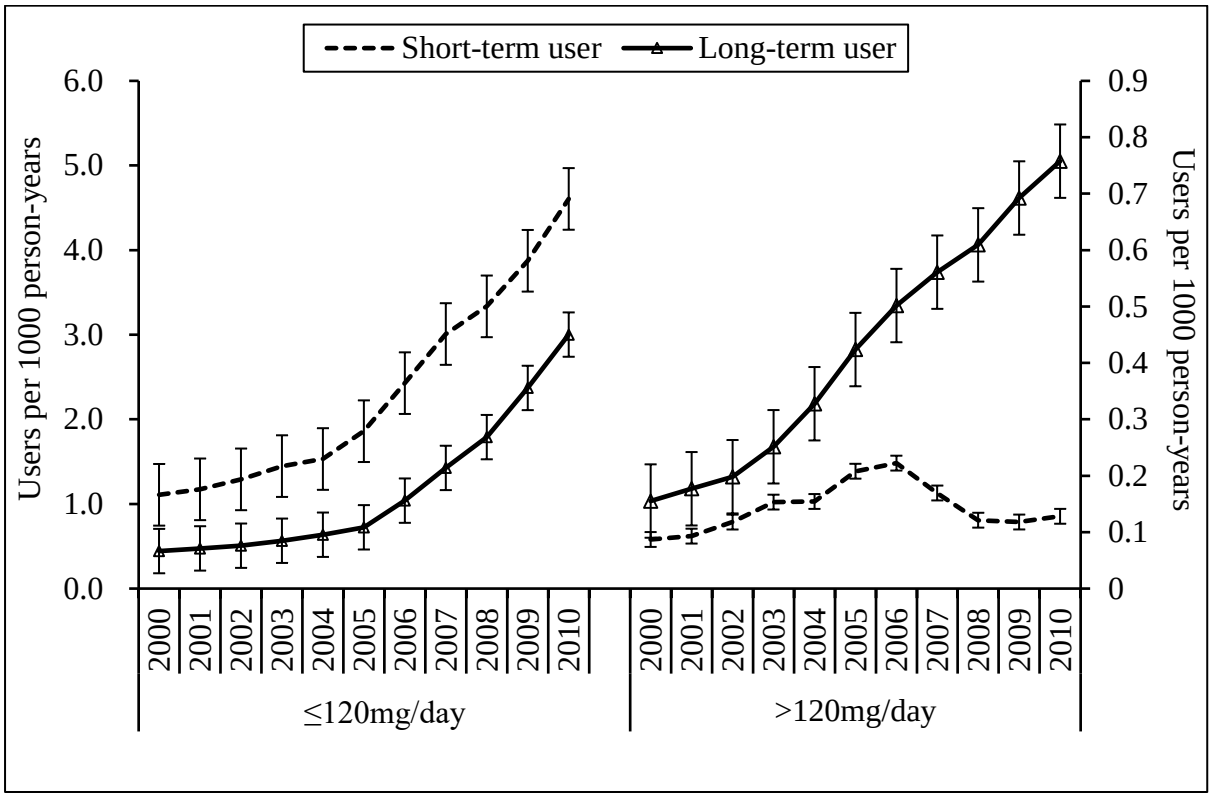
An average oral morphine equivalent daily dose of greater than 120mg was found to be prescribed to 26.01% of long-term users and 6.44% of short-term users. The average high daily dose received by long-term users was 221.19±148.07mg/day, and in short-term users this was 192.87±150.28mg/day (Table 5-7).

Table 5-7 Proportions of users prescribed low and high average (OMED) dose per day

User-group	N (%)	Mean OMED/year mg ±SD	Mean days' supply/year ±SD
Short-term			
≤120mg/day	81,142 (93.56%)	46.56±24.46	26.95±21.25
>120mg/day	5,583 (6.44%)	192.87±150.28	37.17±23.17
Long-term			
≤120mg/day	19,758 (73.99%)	51.22±26.79	240.11±90.42
>120mg/day	6,945 (26.01%)	221.19±148.07	277.05±84.55

Figure 5-3 displays the prevalence of users prescribed high average OMED (>120mg/day) compared to the prevalence of users prescribed low average OMED (≤120mg/day) per year over the 11 years. While a substantially growing prevalence of both short-term and long-term strong opioid users were receiving lower daily doses in each year, an increasing prevalence of long-term users were prescribed high OMED (greater than 120mg/day) per year. This group increased from 0.16 per 1000 person-years in 2000 to 0.76 per 1000-person-years in 2010, representing an APC of 18.36% (95%CI: 16.00, 20.80, p<0.001).

Figure 5-3 Annual prevalence of users prescribed low and high average (OMED) daily dose



5.5.4 Patterns of co-prescriptions with psychoactive and "other" analgesic drugs

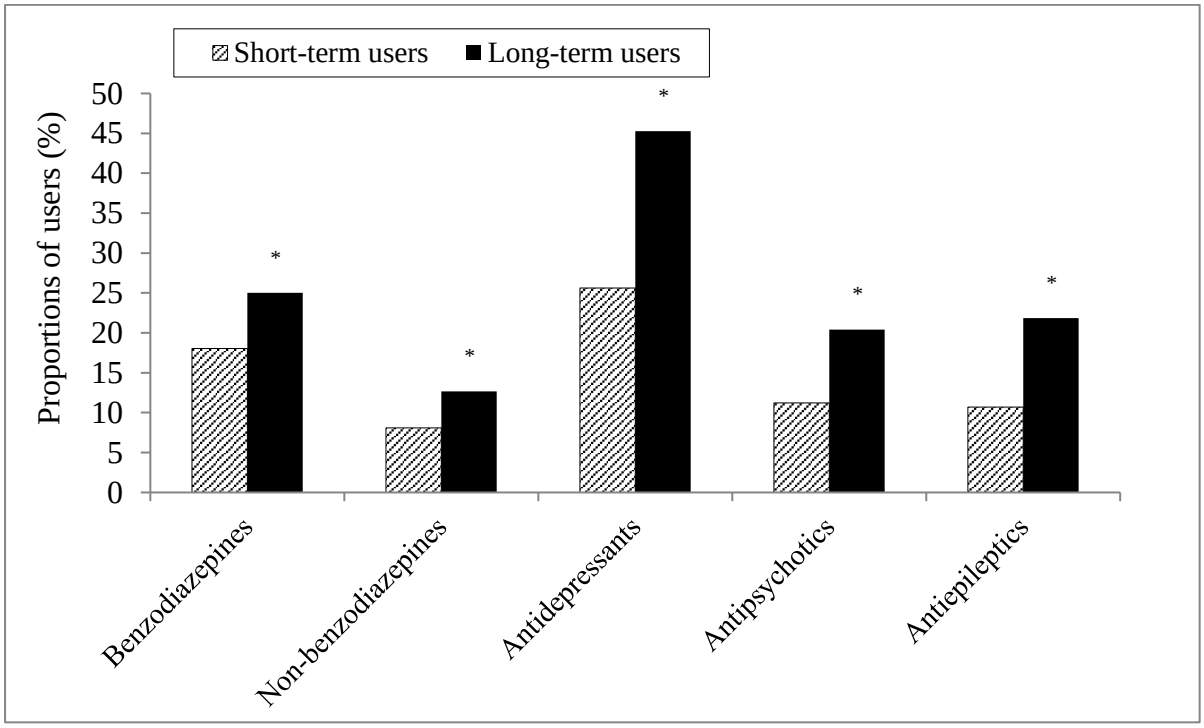
5.5.4.1 Benzodiazepine, non-benzodiazepine sedative-hypnotics

More than a third (37.67%) of long-term users and over a quarter (26.11%) of short-term users were co-prescribed sedatives-hypnotics during the study follow-up. Benzodiazepines were the most frequently prescribed sedative-hypnotics, in 25.00% and 18.03% of long-term and short-term users respectively (Figure 5-4). Compared to short-term users, the average number of days' of benzodiazepine supplied per year was almost two-fold higher in long-term users, with 206.47±131.78 days versus 123.98±126.99 days in short-term users (Table 5-8).

5.5.4.2 Antipsychotics, antidepressants and antiepileptic's

Similarly, antipsychotics, antidepressants and anticonvulsants were more commonly prescribed to long-term users than short-term users (Figure 5-4).

Figure 5-4 Proportions of strong opioid users co-prescribed psychoactive medication



* *p*-values were ≤0.05

Of all long-term users, 45.28% (n=12,090) had received antidepressants, 21.84% (n=5,831) antiepileptics, and 20.42% (n=5,454) antipsychotics. In addition, the average duration of use per year was particularly high amongst long-term users receiving antidepressant and antiepileptics, with 248.41±108.91 days and 231.87±112.38 days' supply, respectively (Table 5-8).

Table 5-8 Average days' supply of psychoactive medication stratified by user group

	Average days' supply/user/year	
Drug class	**Short-term users± SD**	**Long-term users± SD**
Benzodiazepines	123.98±126.99	206.47±131.78
Non-benzodiazepines	142.56±124.93	208.04±128.57
Antidepressants	181.63±121.10	248.41±108.91
Antiepileptics	159.41±121.11	231.87±112.38
Antipsychotics	74.06±96.97	120.91±123.81

5.5.4.3 Weak opioids, NSAIDs, paracetamol, tramadol

The proportions of users that received weak opioids and various non-opioids are shown in Table 5-9. Amongst long-term users, non-steroidal anti-inflammatory medications (NSAIDs) and paracetamol were more frequently prescribed than weak opioids and tramadol, whereas in short-term users, NSAIDs and weak opioids were more common.

Table 5-9 Proportion of users co-prescribed non-opioids and weak opioids

Drug class	**Short-term users**	**Long-term users**	**Test (df)**	**P-value**
NSAIDs	24,629 (28.40)	10,722 (40.15)	$X^2(1)=1.30 \times 10^3$	<0.001
Paracetamol	23,068 (26.60)	10,905 (40.84)	$X^2(1)=2.00 \times 10^3$	<0.001
Weak opioids	24,376 (28.11)	8,848 (33.13)	$X^2(1)=249.17$	<0.001
Tramadol	14,625 (16.86)	5,107 (19.13)	$X^2(1)=72.67$	<0.001

Significance at $p \leq 0.05$

An analysis of durations of supply showed that NSAIDs and weak opioids were prescribed for prolonged periods per year in both user-groups. An average days' supply per year of NSAIDs was 189.22±118.61 days and 130.15±109.72 days amongst long-term and short-term users, respectively. The average days' supply of weak opioids was 159.62±110.73 days and 119.55±103.41 days per year in long-term and short-term users, respectively (Table 5-10). Furthermore, tramadol was also used over prolonged periods more so amongst long-term users than short-term users.

Table 5-10 Average days' supply of co-prescribed non-opioids and weak opioids

	Average days' supply/user/year	
Drug class	**Short-term users± SD**	**Long-term users± SD**
Weak opioids	119.55±103.41	159.62±110.73
Tramadol	113.89±105.88	161.64±113.13
NSAIDs	130.15±109.72	189.22±118.61
Paracetamol	90.58±86.13	141.03±102.04

5.5.5 Covariates influencing long-term use

The odds of users in the study being long-term users in each year during follow-up were influenced by several covariates. The results of the multivariate analysis showed that females (aOR: 1.07 95%CI: 1.04, 1.11), an age beyond 50 years, a high Townsend deprivation score (aOR: 1.13; 95%CI: 1.06, 1.20) and a greater yearly number of GP visits were significantly linked to an increased likelihood of strong opioid users being long-term users per year in the final adjusted model (model B) (Table 5-11). Being a smoker at index date was a significant influencer in the crude unadjusted model (OR: 1.08; 95%CI: 1.03, 1.14), but was no longer significant once other variables were adjusted for in model A and model B.

Amongst the clinical conditions examined in the final adjusted model (B); a diagnosis of musculoskeletal related pain disorder up to 6 months prior to index date, such as back pain, unspecified arthritis, osteoarthritis, neuropathic pain, general spinal pain, fibromyalgia, and ankylosing spondylitis were found to be linked to a 7%, 18%, 21%, 22%, 40%, 45% and 77% increased odds of being long-term strong opioid user in each year of follow up respectively. On the other hand, abdominal pain, headache, sciatica, facial pain, trigeminal neuralgia and postherpetic neuralgia were linked to a reduced likelihood. The presence of osteoporosis as a comorbidity at index date was also positively linked to long-term strong opioid use (aOR: 1.37; 95%CI: 1.23 to 1.53), whereas the co-existence of cardiovascular conditions such as heart failure, atrial fibrillation and stroke were negatively associated with users being on long-term strong opioid therapy. Co-prescriptions with benzodiazepines, non-benzodiazepines, antidepressants, antiepileptics and antipsychotic were linked to increased odds of long-term use, and so was the OMED dose prescribed. An average daily dose greater than 100mg and more than 120mg OMED per year was linked to a 2-4 fold higher odds of long-term strong opioid use.

Table 5-11 Univariate and multivariate analysis of covariates linked to long-term use

Variables (Reference group)	**Unadjusted odds ratio (95%CI)**	**Adjusted odds ratio (95%CI)**	
		Model A [1]	**Model B** [2]
Age (<50 years)			
50-64 years	1.16 (1.11-1.21)***	1.15 (1.10-1.20)***	1.15 (1.10-1.20)***
65-74 years	1.00 (0.96-1.04)	0.99 (0.94-1.04)	1.05 (1.00-1.11)*
≥75 years	0.79 (0.76-0.82)***	0.79 (0.76-0.83)***	1.07 (1.01-1.12) **
Gender			
Females	1.11 (1.08-1.14)***	1.13 (1.10-1.17)***	1.07 (1.04-1.11)***
Region (North East)			
North West	0.96 (0.87-1.06)	1.00 (0.91-1.11)	1.00 (0.90-1.12)
Yorkshire and Humber	0.93 (0.83-1.04)	1.00 (0.89-1.12)	0.98 (0.86-1.11)
East Midlands	0.79 (0.70-0.89)***	0.84 (0.74-0.94)**	0.88 (0.77-1.01)
West Midlands	0.84 (0.76-0.93)***	0.89 (0.80-0.99)*	0.92 (0.82-1.03)
East of England	0.89 (0.80-0.98)*	0.96 (0.87-1.07)	0.98 (0.87-1.10)
South West	0.66 (0.60-0.73)***	0.72 (0.65-0.80)***	0.72 (0.64-0.81)***
South Central	0.72 (0.65-0.80)***	0.80 (0.72-0.89)***	0.80 (0.71-0.89)***
London	0.86 (0.77-0.95)**	0.89 (0.80-0.99)*	0.94 (0.84-1.06)
South East	0.83 (0.75-0.91)***	0.89 (0.80-0.99)*	0.96 (0.85-1.07)
GP visits (1-3 visits/year)			
4-7 visits/year	2.26 (2.17-2.36)***	-	2.06 (1.97-2.15)***
8-11 visits/year	3.24 (3.09-3.40)***	-	2.79 (2.65-2.93)***
≥12 visits/year	4.50 (4.32-4.68)***	-	3.66 (3.50-3.83)***
Townsend score (1-least deprived)			
2	1.02 (0.95-1.08)	1.03 (0.97-1.10)	1.03 (0.96-1.11)
3	1.07 (1.01-1.13)*	1.07 (1.01-1.13)*	1.05 (0.98-1.11)
4	1.12 (1.07-1.18)***	1.10 (1.05-1.16)***	1.08 (1.02-1.14)**
5-most deprivation	1.24 (1.17-1.31)***	1.17 (1.11-1.25)***	1.13 (1.06-1.20)***
Smoking status (non-smoker)			
Smoker	1.08 (1.03-1.14)**	1.03 (0.98-1.08)	1.02 (0.96-1.07)
Ex-smoker	0.93 (0.89-0.98)**	0.98 (0.93-1.02)	0.97 (0.93-1.02)
Obesity (≤30 kg/m^2)			
>30 kg/m^2	1.21 (0.98-1.50)	1.07 (0.86-1.32)	1.07 (0.85-1.35)
Pain diagnoses			
Back pain	1.18 (1.14-1.22)***	1.16 (1.12-1.21)***	1.07 (1.03-1.11)***
Neuropathy	1.68 (1.44-1.96)***	1.65 (1.41-1.93)***	1.22 (1.03-1.45)*
Osteoarthritis	1.32 (1.25-1.40)***	1.29 (1.21-1.36)***	1.21 (1.14-1.29)***
Fibromyalgia	2.25 (1.88-2.70)***	1.88 (1.56-2.26)***	1.45 (1.19-1.77)***
Ankylosing spondylitis	1.89 (1.27-2.81)**	1.72 (1.15-2.56)**	1.77 (1.14-2.74)**
Unspecified arthritis	1.30 (1.16-1.46)***	1.22 (1.09-1.38)***	1.18 (1.04-1.34)**

[1] Adjusted for all covariates except time-varying variables, [2] Adjusted for all variables *$p\leq0.05$, **$p\leq0.01$, ***$p\leq0.001$

(Continued) Table 5-11 Univariate and multivariate analysis of covariates linked to long-term use

Variables (Reference group)	Unadjusted odds ratio (95%CI)	Adjusted odds ratio (95%CI)	
		Model A [1]	Model B [2]
Pain diagnoses			
Spinal pain	1.68 (1.41-2.02)***	1.65 (1.37-1.98)***	1.40 (1.15-1.71)***
Pancreatitis	1.16 (0.92-1.46)	1.30 (1.03-1.65)*	1.16 (0.90-1.50)
Abdominal pain	0.65 (0.62-0.69)***	0.64 (0.61-0.68)***	0.63 (0.59-0.67)***
Colitis	0.73 (0.53-1.01)*	0.74 (0.54-1.03)	0.71 (0.50-1.01)
Menstrual pain	0.14 (0.02-1.00)*	0.14 (0.02-1.01)*	0.14 (0.02-1.04)
Headache	0.74 (0.67-0.82)***	0.72 (0.65-0.80)***	0.64 (0.58-0.72)***
Sciatica	0.77 (0.72-0.83)***	0.68 (0.63-0.72)***	0.64 (0.60-0.69)***
Temporomandibular disorder	0.78 (0.51-1.19)	0.78 (0.51-1.19)	0.70 (0.44-1.09)
Trigeminal neuralgia	0.59 (0.43-0.80)***	0.62 (0.45-0.85)**	0.46 (0.33-0.64)***
Facial pain	0.77 (0.59-1.00)*	0.79 (0.61-1.03)	0.67 (0.50-0.89)**
Postherpetic neuralgia	0.71 (0.51-0.97)*	0.80 (0.58-1.11)	0.65 (0.46-0.92)**
Medical comorbidity			
Osteoporosis	1.39 (1.25-1.53)***	1.44 (1.30-1.59)***	1.37 (1.23-1.53)***
Dementia	0.54 (0.43-0.69)***	0.63 (0.50-0.80)***	0.86 (0.67-1.10)
Heart failure	0.51 (0.44-0.58)***	0.60 (0.52-0.69)***	0.74 (0.64-0.86)***
Atrial fibrillation	0.63 (0.54-0.74)***	0.76 (0.65-0.90)***	0.81 (0.69-0.96)*
Stroke	0.65 (0.57-0.75)***	0.75 (0.65-0.86)***	0.77 (0.66-0.90)***
COPD	0.76 (0.69-0.85)***	0.77 (0.69-0.86)***	0.78 (0.70-0.88)***
Psychiatric comorbidity			
Depression	1.00 (0.89-1.12)	0.95 (0.84-1.08)	0.85 (0.74-0.97)*
Anxiety	1.08 (0.95-1.23)	1.05 (0.92-1.20)	0.87 (0.75-1.01)
OMED/mg (≤50mg/day)			
51-100mg/day	0.74 (0.72-0.77)***	-	0.81 (0.78-0.84)***
101-120mg/day	1.62 (1.50-1.74)***	-	1.60 (1.48-1.74)***
>120mg/day	4.01 (3.84-4.20)***	-	3.59 (3.42-3.77)***
Co-prescribed drugs			
Antidepressant	2.48 (2.41-2.55)***	-	1.80 (1.75-1.86)***
Benzodiazepines	1.51 (1.46-1.56)***	-	1.07 (1.03-1.11)***
Non-benzodiazepine	1.67 (1.60-1.75)***	-	1.16 (1.10-1.21)***
NSAID	1.59 (1.55-1.64)***	-	1.13 (1.09-1.17)***
Paracetamol	1.98 (1.93-2.04)***	-	1.54 (1.49-1.60)***
Weak opioids	1.11 (1.07-1.14)***	-	0.79 (0.77-0.82)***
Tramadol	0.96 (0.93-1.00)*	-	0.61 (0.58-0.63)***
Antiepileptic's	2.50 (2.41-2.59)***	-	1.70 (1.63-1.77)***
Antipsychotic's	1.42 (1.36-1.49)***	-	1.07 (1.02-1.12)**

[1] Adjusted for all covariates except time-varying variables, [2] Adjusted for all variables

All independent variables except GP visits and co-prescriptions were measured up to 6 months prior to index date, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$

5.6 Discussion

5.6.1 Main findings

This longitudinal study sought to better understand the treatment patterns with strong opioids in a sample of long-term users versus short-term users of the potent analgesics. Collectively the study sample made up 83.44% of the baseline population of non-cancer pain patients prescribed one or more strong opioids between 2000 and 2010. The remaining proportions of users (16.56%) were episodic users (i.e. users of strong opioids over short and long-term periods) and were excluded from the study analysis. It is generally suggested that applying a stringent participant selection criteria in any analysis can limit the representativeness of the study sample and generalizability of findings [356]. However, in the current study episodic users represented a substantively small(er) sample throughout the study follow up with the population selected for study representing a larger sample. Hence, this ensured that the external validity of the analysis and findings were maintained and not undermined.

The average follow-up duration of long-term users was 4.48±3.02 years, with a range of 1-11 years. Compared with short-term users who had an average days' supply of at least one month per year (27.57±21.51 days) long-term users received strong opioids over an average of 8-months (249.81±90.39 days) per year, which almost covered a daily supply per year.

The mean daily oral morphine equivalent dose (OMED) of long-term users (95.88±109.03 mg/day/year) was almost twice that of short-term users (54.80±54.55mg/day/year). Almost a third (26.01%) of long-term users were prescribed high daily doses of strong opioids during follow-up. Their annual mean OMED was 221.19±148.07mg/day and the mean duration of supply was 277.05±84.55 days/year (9 months/year). Long-term users were more likely to receive additional medications known to adversely interact with opioids. Of these

benzodiazepine-based sedatives and hypnotics, antidepressants and antipsychotics were used for long periods and on average greater than 90 days/year.

After adjusting for age, gender and geographic region in the final model of the multivariate analysis: high Townsend deprivation score, greater annual numbers of GP consultations and several chronic pain conditions including back pain, neuropathy, osteoarthritis, fibromyalgia and co-prescriptions of psychoactive medications including benzodiazepines, antidepressants and antipsychotics were found to be significantly associated with long-term strong opioid use. The small difference in the odds-ratios in the GEE Model A and B meant that the baseline factors of age, gender, socioeconomic status and specific pain and comorbid diagnosis remained strong predictors of long-term strong opioid use irrespective of the adjustment of time-varying variables.

5.6.2 Prescribing patterns

5.6.2.1 Frequency of prescriptions per year and number of days of drug supply

Previous international (longitudinal prospective) studies have found that 90 days of use to be an important point in opioid use. This is because once 90 days of opioid therapy is reached (which is equivalent to only three prescriptions of one-month supply of each) patients are more likely to remain on opioid treatment for prolonged periods and the outcome of opioid use becomes less clear [137, 336, 357-360].

Two main studies in particular have documented this. Martin BC et al. (2011) identified adult non-cancer pain patients prescribed opioids from two large US insurance claims database between 2000 and 2005 [357]. Patients were followed from their first chronic opioid use (>90 days) until discontinuation, death or study end. The study found a linear increase in opioid use

following the initiation of long-term use. Of the 23,419 study participants two thirds (65% and 67% in the two insurances) remained on continuous opioid therapy beyond 90 days at the end of follow up, and they were less likely to discontinue treatment and had a mean duration of approximately 2 years. The study emphasized that the 90-day mark was a crucial level to indicate no return from chronic opioid use, and that the use becomes self-perpetuating.

The second study was conducted by Braden et al. (2008) who used a similar insurance database and study time-line (2000-2005) as Martin BC et al. (2011) to examine the utilisation of opioids in four pain conditions, which included: arthritis/joint pain, back pain, neck pain, and headaches [360]. Overall, the percentage of patients with any opioid use and 90 days' use were found to have increased between 2000 and 2005. Noticeably, patients who were prescribed 90 days in 2000 were more likely to be on greater than 90 days in 2005, regardless of the pain condition treated.

The exposure of opioids long-term is inevitably associated with the possibility of predisposing patients to unnecessary opioid-related adverse effects that are inherent to the drug class, including tolerance and hyperalgesia [176, 179, 180]. Moreover, studies that have addressed chronic opioid therapy have found that patients on continuous long-term use of opioids compared to patients using the drugs intermittently over short-term periods tended to report higher pain intensity, disability, and an apprehension towards the prospect of medication-tapering in the absence of significant benefits (primarily due to the fear of withdrawal symptoms or worsening of pain) leading to a long-lasting use of the drugs [161-167].

5.6.2.2 Daily oral morphine equivalent dose

The study reported a year-on-year steady increase in the average daily dose in oral morphine equivalent until 2005, with a peak in the average daily dose of 119.07±119.06mg/day amongst long-term users, before levelling off from 2005 till 2010. Although the exact reason behind the escalation cannot be deduced, the pattern observed may have reflected a growth in the attentiveness and response of prescribers to manage CNCP. This may have plausibly been influenced by initiatives that were aimed at raising awareness of pain and its management, such as the introduction of Pain as the fifth vital sign, which was originated by the American Pain Society (APS) and later advocated by the Royal College of Surgeons and Anaesthetists in 1996 [361, 362]. This initiative recommended that pain should be routinely assessed in clinical practice and form an integral part of patient management.

Meanwhile, the marginal stagnation in the average daily dose observed beyond 2005 could be interpreted in light of several national clinical guidelines produced at this time and beyond, which provided guidance on the early and long-term management of pain, but also encouraged the use of non-opioids prior to opioid use [55, 57, 58]. Having said this, conversely, in the analysis, the average daily dose pattern occurred in parallel with a consistent increase in the average number of day's supply, suggesting continual exposure and a continued haunting safety concern.

Concurrently, international based research investigating the prescribing patterns of opioids in non-cancer pain has indicated an escalation in opioid-dose to be frequent and unavoidable with prolonged treatment. Franklin GM et al. (2009) conducted a recent cohort study of workers in Washington state with back injury who were treated with opioids and found that within a year

of the workers' injuries, the strongest predictor of long-term opioid use was oral morphine equivalent dose [358].

Patients prescribed 40 mg of morphine equivalent (MED) per day in the first quarter of the workers' injury claim had 6-fold higher odds of continued opioids use long-term. The MED amongst long-term users continued to significantly rise ($p<0.001$) between the first and fourth quarter by 61.76% (from an average of 2364mg to 3824mg, respectively). Meanwhile, very few patients had a clinically significant improvement in pain and function.

In a different study, Cifuentes M et al. (2010) also used a workers' insurance database to study duration and dose patterns of weak and strong opioids that were prescribed to patients reporting disabling low back pain [363]. The study followed a cohort of patients for up to 2 years from the start of their opioid therapy in 2002. Out of the 2,868 patients who were prescribed opioids, 70% had received the medicine within a month of reporting work-related low back pain, implying early opioid use, and at the end of the study over a third of the patient were still using the analgesics. The study conducted a longitudinal regression analysis and found a significant association between the initial dose use of opioids and subsequent dose increases. It was approximated that in each consecutive week of opioid use the dose rose by 0.7%, and by the end of the 2 years, the average dose used was two-folds higher than the initial prescribed dose. In addition, while the prescribing of weaker opioids decreased during the 2-year intervals, the prescribing of stronger opioids remained constant and predominated in the long-term.

In the current study, a higher daily morphine equivalent dose beyond 100mg was linked to a predictable likelihood of users becoming long-term users compared to the use of ≤50mg/day. Furthermore, users on a daily dose of 101-120mg were 60% more likely to be long-term users

per year, and those who received greater than 120mg/day were four times more likely to use strong opioids long-term. The relationship between high daily dose and long-term opioid use observed in this study may indicate insufficient analgesia or the development of tolerance. It may have also indicated difficulty in managing pain condition(s). However, the control of a wide range of pain conditions and comorbidities in the multivariate analysis revealed that high dose use remained significantly linked to long-term use, signifying that the use of high morphine equivalent daily doses occurred regardless of the type of pain diagnosis.

The use of opioids at high doses has been highlighted as a major concern, particularly in recent years, and studies have shown a linear relationship between high daily doses of opioids and abuse, dependence and overdose. Dunn KM et al. (2010) showed that a use of 100mg/day of opioids for more than 90 days in conditions such as neck, back pain and arthritis were linked to almost a 9-fold increase in the risk of overdose (HR: 8.87, 95%CI: 3.99 to 19.72), and patients prescribed 50-99 mg/day had a 3.7-fold (95%CI: 1.47 to 9.50) increased risk of overdose [185]. This has been echoed by a number of other studies, which have emphasised the need for further research into the harms associated with chronic opioid doses, and their preclusion [364-366].

Moreover, Baldini A et al. (2012) reviewed recent evidence on adverse effects of long-term opioid therapy in non-cancer pain from peer-reviewed published journals from 2005 to 2011 [367]. He concluded that opioids might exert dose-dependent adverse effects to a number of diverse organ systems that include the gastrointestinal, respiratory, musculoskeletal, and endocrine systems. Such effects include; ataxia breathing, which was observed in 61% of individuals who were using opioids at a morphine equivalent dose of 200mg compared to 5% in non-opioid using patients. A 1.4 relative risk of fracture was noted amongst elderly patients

on doses over 50mg, and a dose-dependent risk of opiate induced androgen deficiency (hypogonadism) and sexual dysfunction was also described.

More recently, Huffman KL et al. (2017) carried out an observational study of patients on chronic high-dose opioid therapy (>100mg/day) to investigate the impact of gradual reduction and discontinuation of opioid therapy [368]. The study, which was carried out in a specialised interdisciplinary setting, measured key outcome components such as pain intensity, physical and neuropsychological functioning prior to the intervention, and at 6-12 months following the weaning procedure. The results identified a startling improvement in patients' pain severity, physical function and mood immediately after opioid-use reduction, which was maintained following discontinuation of the therapy and during the study follow up. The intervention provided continuous support to patients through the use of psychotherapy, educational and medicine management strategies.

5.6.2.3 Co-prescriptions

Polypharmacy with antidepressants, antipsychotics and sedatives-hypnotics were prevalent amongst the strong opioid users. In particular, almost 40% of long-term users had a sedative-hypnotic prescribed during the follow up period. These drugs were associated with increased odds of long-term use.

The greater use of sedative-hypnotics with long-term opioids is at odds with clinical guidelines, and is contrary to many expert recommendations [288, 330, 332, 333]. Benzodiazepines tend to enhance the CNS effect of opioids and boost the positive subjective impact of opioids, resulting in a state of euphoria, and the synergistic effects of the combination can also lead to risks of respiratory depression, overdose, increased addictive behaviour and sedation. While reviews

show a potential role for benzodiazepines in acute pain, little evidence supports their use in chronic pain.

Nielsen S et al. (2015) assessed benzodiazepine use in a large cohort of chronic non-cancer pain patients prescribed opioids [369]. Patients were stratified into four groups; patients never prescribed benzodiazepines (36.9%), patients with a previous history of benzodiazepine use (30.5%), patients using benzodiazepine infrequently (less than a daily use) (15.2%), and patients on daily benzodiazepine use (17.3%). The result that emerged was that, compared to patients who were never prescribed benzodiazepines, patients using benzodiazepine either infrequently or on a daily basis were inclined to be prescribed high opioid doses of greater than 200mg/day oral morphine equivalents.

The study also found that benzodiazepine use was associated with greater reporting of moderate to severe depression and anxiety. Moreover, patients' co-prescribed benzodiazepines were also more likely to be prescribed antidepressants and antipsychotics. The authors concluded that the use of benzodiazepine affects opioid dose use in chronic non-cancer pain patients, and that this requires additional attention in the management of chronic non-cancer pain patients who are prescribed opioids.

In the current study, long-term users who received benzodiazepines were found to have almost twice the average daily dose (OMED) of strong opioids (113.51±129.19 mg/day) compared to long-term users who had no benzodiazepines (89.21±99.54 mg/day) during the follow-up period. However, it was not clear if the high use of sedative-hypnotics was due to treatment of pre-existing anxiety, sleep disorder, or sleep disorders instigated by the opioid use.

Nevertheless, the prevalence of the co-prescribed medications, particularly that of psychoactive medications, demonstrates that long-term strong opioid users' management is not approached from a single pharmacological treatment, and that a wide variety of medications are used to address the needs of these patients. This highlights, and perhaps raises the significance of, a comprehensive approach to pain management, particularly in sub-groups of patients on long-term opioid treatment.

5.6.3 Traits associated with long-term strong opioid use

Apart from dose and co-prescriptions of psychoactive medications, a number of sociodemographic and clinical factors measured at index date were found to influence long-term use in this study. Deprivation was found to be a significant influencer in increasing the likelihood of long-term strong opioid use by 24% in the unadjusted model and 13% in the adjusted analysis (Model B).

This is consistent with previous international studies. A study by Ndlovu M et al. (2014) reported lower likelihood of analgesic prescriptions being written for patients in least deprived areas (OR: 0.69; 95%CI: 0.55, 0.86) [370]. The author suggested that this could be due to a reliance of low-income patients on analgesics that are available over the counter, which are available without prescriptions. Another study by Volinn E et al. (2009) identified a relationship between opioid use and employment. The study identified a 6-fold increase in long-term work loss amongst non-cancer pain patients prescribed >90 days of opioid prescription compared to non-opioid users [336]. The author pointed out that the presence of chronic pain could lead to long-term opioid use, but also the presence of chronic pain could increase the risk of incapacity to work, which would affect patients' socioeconomic status, suggesting a circular relationships.

The relationship between smoking and strong opioid use observed in the current study has been previously documented in international studies. Though the mechanism underlying the association is unclear, proposed explanations have oriented towards the influence of nicotine withdrawal on hyperalgesia, which transpires subtly between times of inactive smoking. Indeed, animal studies have indicated that nicotine use modulates the endogenous opioid system [280, 343, 351, 352]. Nicotine use has also been linked to the attenuation of cross-tolerance with opioids, potentially enhancing opioid consumption requirement [371]. However, the association of smoking and long-term strong opioid use did not remain significant in the model that included various patient clinical and demographic factors in the present study, suggesting that nicotine use may not have an independent effect on strong opioid utilisation.

Additionally, both age and gender were related to chronic opioid use. Being female was associated with a 7% higher risk of using strong opioids long-term. Although gender difference in strong opioid prescription use in the literature is sparse, the identification of higher risk of chronic strong opioid therapy in females is consistent with a number of longitudinal studies that have assessed characteristics, and their relationships to analgesic use [335, 338, 339, 348].

Specifically, it is likely that the higher prevalence of long-term strong opioid use in females is somewhat related to the prevalence of symptomatic psychiatric illnesses, including depression and the multiplicities of pain, as detected in this subgroup in chapter 4 (pages: 125, 127). However, studies that have adjusted for important confounders by indication have highlighted an increased risk of problematic opioid use with long-term opioid therapy in patients with psychiatric distress, and have implied that long-term opioid therapy in chronic pain ought to also be understood in the light of the multifaceted psychological state of patients [318, 319].

Several long-term pain disorders were significantly associated with long-term strong opioid use in the cohort of patients studied. Back pain, osteoarthritis and fibromyalgia were conditions most significantly and consistently associated with long-term strong opioid therapy in all three multivariate regression models. Patients diagnosed with these pain conditions prior to strong opioid prescription use were 7%-45% more likely to continue treatment following prescribing. Distinctively and perturbingly, experimental trials have demonstrated that opioid dependence tended to arise at different time-points in different chronic pain patients, with back pain patients developing dependence after only 1-3 months of daily use of opioids [(372)].

Meanwhile, general comorbidities such as cardiovascular conditions (heart failure, atrial fibrillation, and stroke) were found to decrease the likelihood of long-term use, suggesting the deployment of cautionary drug use in these conditions. Previous studies have provided a possible indirect explanation to this through the reported negative relationship between circulatory diseases, pain regulation and reduced pain sensitivity, both in hypertensive (>140/90mm Hg) and in normotensive patients alike [(373-375)].

5.6.4 Strengths and limitations

To the best of our knowledge, this is the first UK primary care-based longitudinal study to follow non-cancer pain patients from their initially prescribed strong opioid(s) to quantify long-term prescribing patterns of strong opioids in relation to short-term strong opioid use, as well as identifying factors influencing users being strictly long-term users per year, while adjusting for various time-varying and time-invariant factors.

The advantages of using such data and analysis technique used is that the use of large numbers of data points increases the degrees of freedom, decreases the correlations between explanatory

variables, and hence ensures a more consistent and unbiased estimate in analysing the data. In addition, the GEE model used was able to account for the time-varying nature of the exposure variable (strong opioid use) and estimate covariates of influence. However, this study remains to be an observational study, and like many other observational studies examining relationships with medical exposure, the relationship between exposure and covariates should be looked at as associations, and not as causal relationships. The study sought to explicitly examine relationship of a number of patient-related factors to long-term strong opioid use; however, it is to be noted that practice and physician-related factors could also have been an influence, though the limitation is that neither of the variables are readily recorded or available in CPRD database.

5.6.5 Conclusions

Compared with short-term users who used strong opioids for at least a month per year, strong opioid use long-term appeared to be linked to age, female gender, high deprivation, greater GP visits and co-prescriptions of psychoactive medications. Furthermore, amongst long-term users, a subgroup received high mean daily doses per year that was 1.5-2 times greater than recommendations in British guidance. Knowledge of patient factors that affect the propensity of long-term use provides useful information for identifying needs, and for planning and monitoring patient care.

Chapter 6 Primary and secondary healthcare use of non-cancer pain patients prescribed long-term strong opioids

6.1 Introduction

Critical reviews of the UKs' healthcare system in recent years have highlighted the continued challenges that the healthcare service face due to continued increase in demand. Health service use has increased significantly, and data provided by NHS England conveys the magnitude of the change over time. Accordingly, between 1999 and 2008, the average number of GP visits made per patients per year increased from 4.1 to 5.5 [376]. More recent figures show a continuation in the increase in GP face-to face consultations by 3.3 per cent between 2010/11 and 2014/15, and a rise in emergency admissions to hospital in England from 18.8 million in 2005–2006 to 22.4 million in 2014–2015 [377, 378].

Set against this, a major focus in a number of recent NHS policies has been to manage the utilisation of primary care but also manage high cost services such as hospitalisation. Concerns have been raised over the financial demands of funded services, with data showing overspending in healthcare expenditure. As detailed by Murray R et al. (2014), between 2013-2014 overspending was reported by the NHS Trust Development Authority resulting in a net deficit of the NHS trust of £241 million, which represented a 5% deficit compared to the financial year of 2012/2013. Furthermore, by the end of 2014, a quarter of all trusts were in deficit [379].

Information on primary and secondary healthcare use nationally is routinely collected and presented by organisations such as NHS England [377]. Estimations of the impact of a number of long-term conditions on the healthcare service are recognised; however, less clear data exists on the healthcare use of patients living with chronic pain and who are managed therapeutically in primary care. One large study by Belsey J et al. (2002) examined a cohort of patients defined

from the MediPlus GP database who were treated with non-steroidal anti-inflammatory and non-opioid based analgesics over a 12 months period (2000-2001) [43]. To establish the characteristics of the workload, both in terms of the number of GP consultations and the delivery of healthcare, cost of utilisation was measured. The study standardized findings to the UK national level and indicated that patients accounted for a total of 4.6 million practice consultations per year at an annual overall cost of £69 million.

Patterns of concurrent healthcare use of patients managed with opioids and stronger opioids are less well-known. On the contrary, healthcare resource use of opioid treated CNCP patients has been the subject of research outside the UK, more so in the USA. Such studies have found that non-cancer pain patients using opioids long-term contribute to a greater healthcare use, and suffer complications that require further medical assistance, such as hospitalisation [380-383]. However, it remains unclear as to whether similar observations are observed in the UK. Thus, characterising patterns of healthcare service use and identifying patients among strong opioid prescribed users who may be prone to higher utilisation of primary healthcare, and users who experience health complications that result in hospitalisation, could be helpful in informing and instigating risk management strategies to better manage patients.

6.2 Aims and objectives

The purpose of this study was to explore patterns of healthcare use of strong opioid users, and in order to avoid confusion with short-term treatments, patients studied were limited to users on long-term treatment. A secondary aim was to identify factors related to the frequency of GP consultations and risk of hospitalisation.

The objectives of the chapter were to:

Primary healthcare

1. Estimate the number of primary care consultations per user per year and identify patient factors influencing GP visits per year.

Secondary healthcare

1. Estimate the proportion of users referred to pain management specialist and identify strong opioid treatment patterns of referred users compared to non-referred users.
2. Identify patients with all-cause in-patient hospitalisations and determine the differential characteristics of in-patient hospitalised users versus non-hospitalised strong opioid users.
3. Determine the average annual number of admissions per user, the cause of admissions/re-admissions and the number of days of hospital stay per user.
4. Identify covariates, including socio-demographic, clinical traits and patterns of strong opioid use associated with the risk of all-cause in-patient admissions.

6.3 Method

6.3.1 Study designs and data source

This retrospective longitudinal study used CPRD database linked with the Hospital Episode Statistics to examine primary and secondary healthcare use from January 2000 to December 2010.

6.3.2 Structure and content of HES database

The HES database was established in 1987 following a report on the collection and use of hospital activity, which was published by a steering group chaired by Dame Edith Körner [384]. The data in HES is collected and managed by Northgate Information Solutions on behalf of NHS digital (formerly known as the NHS Information Centre for Health and Social Care), and is initially submitted to Secondary Uses Services (SUS) before it is obtained by HES. The SUS, which is a secure data storage warehouse, acts as the mediator of information and sends extracts of data at predetermined dates on a monthly basis. A series of validation checks and cleaning stages of the data takes place once the information is received by HES before it becomes accessible for research [385].

The HES dataset contains demographic information, such as age, gender, region of residency, as well as medical diagnosis, interventions and administrative information (such as admission date and discharge date) of all patients that have had hospital care [384].

The HES dataset is linked to CPRD through NHS digital, and the linked dataset consists of five files that are primarily subdivided into “hospitalisation” and “episodes”. While “hospitalisation” refers to the overall time of in-patient stay, “episode” is the time period of

consultation care during hospitalisation. Patients may have several episodes for each hospitalisation [386].

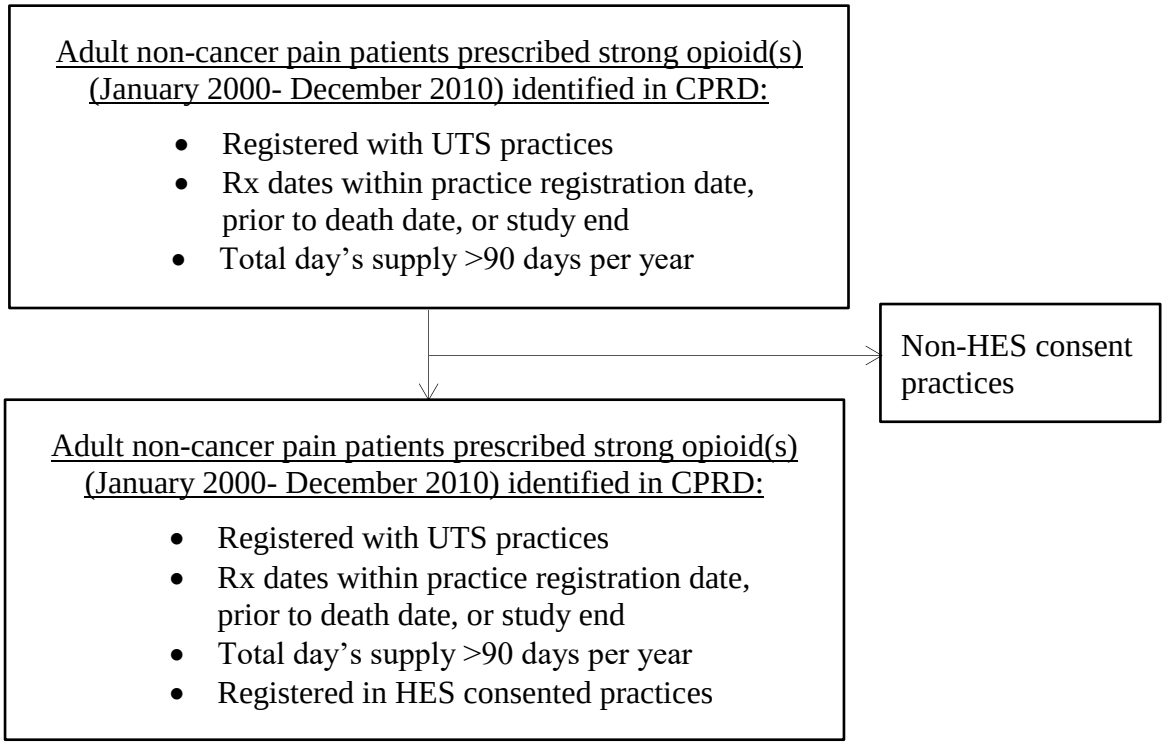
Data on in-patient hospitalisation have been available in HES since 1989, and the data are recorded for each fiscal year, with over 12 million new admissions added each year. All diagnoses in HES are coded using the International Classification of Diseases, 10th revision (ICD-10). This is a standard diagnostic coding system created by the World Health Organization to aid in the recording of clinical information [387]. Episodes may have up to 20 ICD-10 diagnoses, of which one is the primary code or the primary cause of admission(s), investigation(s) and treatment(s), and the remaining codes are secondary codes of diagnoses [387].

This study used HES dataset to estimate in-patient hospitalisation and determine primary causes of admissions and duration of in-patient stay of the study population.

6.3.3 Study population

The sample of patients examined in this study consisted of adult non-cancer pain patients prescribed strong opioids between 2000 and 2010, and who were identified in chapter 5 (page 143) as long-term users. These were users who were followed from the index date (first prescription use) on or after 1st January 2000 till 31st December 2010, and who had greater than a total of 90 days of strong opioid supply in each year during follow-up. In order to identify long-term users who had a record of in-patient hospital admission(s), CPRD data was linked to HES hospital in-patient admission dataset (Figure 6-1).

Figure 6-1 Identification of study population in HES database: inclusion criteria



The study sample of long-term strong opioid users registered with HES-consenting practices was determined in two stages. Firstly, practice identifiers were attained from the last three figures of the users' practice code in CPRD. The identifiers were matched with a list of HES practice identifiers, and users with practices registered with HES were determined. Users' hospital admission information was identified in HES data using users' patient identifiers, which were the same patient identifiers in CPRD. Only users with hospital records that were within users' registration date, up to research standard, before users' practice transfer out date or death date and within the years of users' strong opioid prescription use during follow up were included in the analysis.

6.3.4 Study outcomes

Outcome measures for this study were primary healthcare utilisation, pain management referrals and secondary care in-patient admissions. Individual users were followed from their first prescription use (index date) until the end of follow-up, which consisted of either end of the study period (31st December 2010), patients' practice transfer out date (and thus transfer out of the dataset) or patient's death date, whichever occurred first. All outcomes were measured during the follow-up period.

6.3.4.1 Primary healthcare use

Primary care utilisation included in-practice consultations, home visits and telephone consultations. Information on GP visits and consultations were identified from the consultation file in CPRD using Read codes. Annual prevalence of primary care consultation was defined as the sum total of consultations per year and the number of patients consulting primary care at least once during follow-up. The number of consultations per user per year and durations of consultations in minutes were also sequentially determined. Due to the non-normal distribution of the consultation-data, median instead of mean were estimated for the measures (Appendix 20).

6.3.4.2 Pain specialist referrals

Referral of long-term users to pain management services was determined to assess the commonness of the utilisation of the service. Referrals to pain specialists were identified in CPRDs' referral file, using relevant Read codes (Appendix 21). Data on GP referrals to specialist clinics are available in CPRD for the first referral of care only, and any subsequent follow-up appointments organised by the clinic are not recorded. Thus, the total annual number of referrals and proportion of users referred identified denoted initial service use.

6.3.4.3 Secondary care: in-patient admissions

Another outcome of interest was cause of hospital admissions. All In-patient hospitalisations were identified annually for each user following the index date and during the follow-up period. The primary causes of admissions were identified through the application of WHOs' International Classification of Diseases (ICD-10), which categorizes diagnostic causes of admissions into related body systems, such as diseases of the immune system, digestive system, reproductive, nervous system, circulatory system, musculoskeletal system, endocrinology etc. (Appendix 22). The crude total number of in-patient admissions was calculated annually for the overall study sample during follow-up.

Moreover, annual prevalence of long-term users admitted to hospital for in-patient care during the 11 years was determined as a percentage by dividing the number of users with one or more records of in-patient admissions by the overall number of long-term users in the study. The length of in-patient hospital stay was also determined for the study population during follow-up.

6.3.5 Study covariates

Healthcare resource use by non-cancer pain patients prescribed long-term opioid therapy has been highlighted in previous international studies to be affected by several patient-level factors such as demographics, comorbidities and concurrent medication use [319, 339, 348, 381, 382]. Factors that were included in this study were based on the findings of these studies.

Factors included were: users' demographics, such as age, gender and socioeconomic status; disease status related to pain conditions and comorbidity (defined by QOF); lifestyle indicators,

such as smoking, BMI; and medication use patterns, such as oral morphine equivalent daily dose and co-prescribed medications.

The method of extraction and management of covariates was comparable to the method described in chapter 5 (page: 146). Moreover, as in chapter 5, covariates were identified and subdivided into time-varying and time-invariant variables. Socio-demographics, pain-related conditions, long-term comorbidities (measured up to 6-months before index date) and lifestyle factors were included in the analysis as time-invariant variables, whereas oral morphine equivalent daily dose and co-prescriptions with antidepressants, benzodiazepines and non-benzodiazepine hypnotic-sedatives, antipsychotics, as well as non-steroidal anti-inflammatory drugs, paracetamol, anticonvulsants, weak opioids and tramadol were included as time-varying variables.

6.4 Data analysis

6.4.1 Primary analysis

Descriptive statistics including proportions, mean±SD or medians (interquartile range) were used to report on the outcome measures. Joinpoint regression was used to fit a log-linear model of the outcome measures between 1st January 2000 and 31st December 2010, and was used to determine the significance of changes in the outcomes over time. A maximum of one joinpoint was used to model the time trend of each of the outcome variables over time, and the significance level for permutation tests was $\alpha=0{\cdot}05$. The annual percent change (APC) in the trend line of each of the outcome variables was estimated, and the associated 95% confidence intervals were presented [251, 252]. P values of ≤ 0.05 were considered as significant.

Additionally, for primary health care use, a subgroup analysis was preformed to determine the trend in the consultations by age (18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84 and ≥85 years) and gender over time. This was conducted in the interest of determining the contribution of age-gender specific strata to the overall primary care usage during follow-up.

Moreover, to examine and compare patients' demographics and clinical traits between those who had one or more hospital in-patient admissions during follow-up versus strong opioid users with no admissions, unadjusted bivariate statistical tests (X^2) were performed. Treatment patterns in terms of average OMED/user/year and average days' supply/user/year were calculated and compared between hospital admitted and non- admitted users.

6.4.2 Secondary analysis

6.4.2.1 Analysis of association between study covariates and study outcomes

The relationship between the study covariates and the outcome measures were determined in two stages.

Firstly, the association with the outcome measures were examined for each covariate in a univariate regression analysis (crude unadjusted estimates). Since both outcome measures of GP consultations and in-patient hospital admissions were repeatedly measured per year, standard regression methods, such as linear and logistic regression, were not suitable and a univariate generalized estimating equation was used as an alternative to univariate linear regression to determine the relationship of each of the covariates to GP visits and admissions. GP visits and in-patient admissions were entered as dependent variables in the regression model, and as binary variables (≤3 visits/year=0 and >3 visits/year=1, <1admissions/year=0 and ≥1 admissions/year=1, respectively).

Secondly, a multivariate model was generated which included all the covariates that were significant in the univariate model. Similar to the univariate analysis, to account for autocorrelation of in-patient hospital admissions data and GP visits, and the clustering of the data at patient and practice-level, multivariate analysis using generalized estimating equation approach was used. This type of analysis is commonly used when examining the predictors or associates of health care utilisation [226, 388]. In this study, GEE model with binomial distribution, and with a logit link function, was conducted to specify the binary nature of the dependent variables. An independent working correlation structure was assumed for the GEE model (Appendix 19).

The use of ≤3 GP visits per year as a (minimum) reference point in the univariate and multivariate analysis was based and informed by a large national report by the NHS digital in 2009, which showed that the median GP consultation per person per year in England was 3 in 2000 and the rate remained almost constant till the end of 2008. Thus, in the absence of a prioir reference/cut off value for the study population a starting consultation rate similar to the national level was thought to be appropriate to be used as a baseline reference rate in the analysis of outcomes [376].

Lastly, time to in-patient re-admission (in number of days) following discharge from the first recorded admission within the study follow-up time was assessed using Kaplain-Meier curve. Multivariate analysis using GEE was used to determine covariates linked to the risk of re-admission during follow-up (coded as binary variable of 0=no re-admission and 1=re-admission).

The results were presented as adjusted-odds ratios (aOR) (for GP visits) and unadjusted and adjusted risk ratios (aRR) (for admissions) with 95% confidence intervals (95%CI). A p-value of ≤0.05 was considered statistically significant. The analyses were conducted using STATA, version 14.0 (Stata Corporation, College Station, TX, USA) and Joinpoint Regression Program, version 4.5.0.1

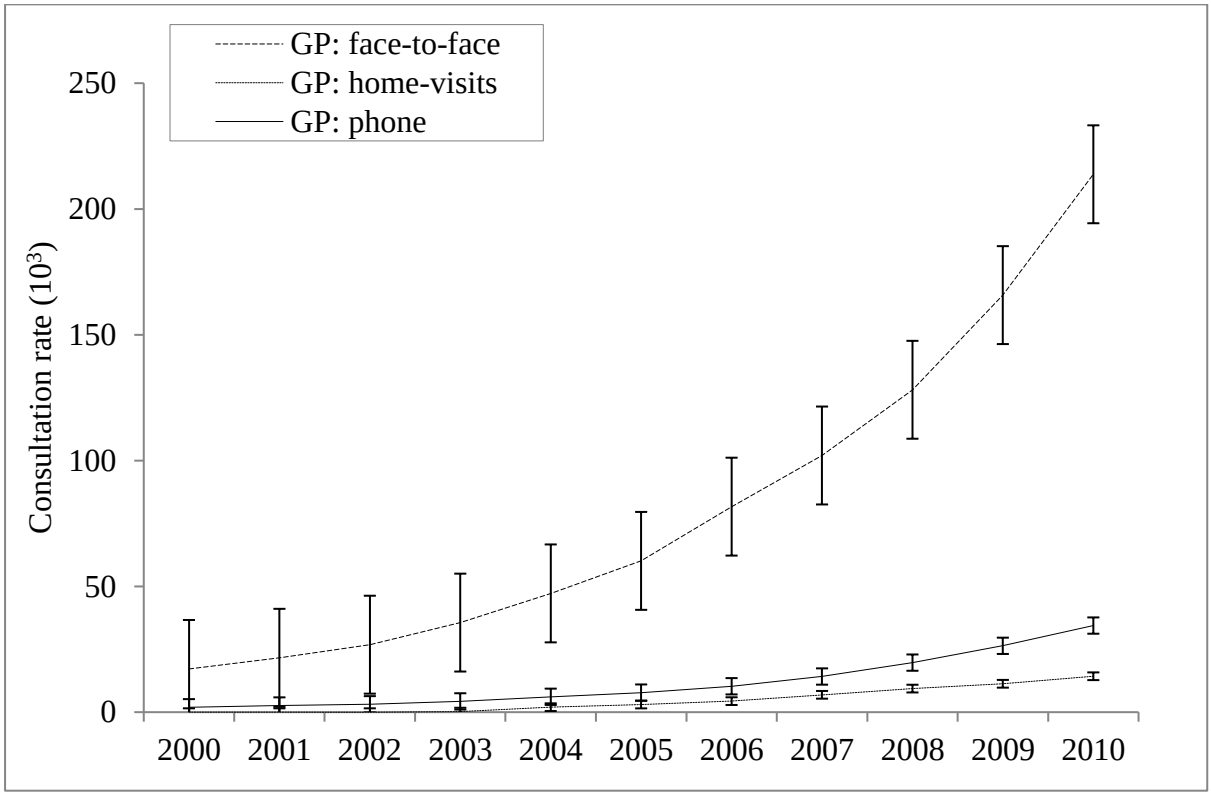
6.5 Results

6.5.1 Primary care consultations

The dataset comprised of a total of 1,082,275 primary care consultations made by the study sample of long-term strong opioid users over the 11-year follow-up. The number of consultations rose annually by 30.61% (95%CI: 29.70, 31.50, p<0.001) from n=19,130 consultations in 2000 to n=262,488 in 2010.

Most consultations were face-to-face GP visits, and this accounted for 83.15% (n=899,932) of all consultations. However, there were marginal changes in the type of consultation over time. In 2000, 89.81% of consultations were face-to-face practice consultations and 10.19% were telephone-based consultations. By 2010, 81.45% were surgery visits, 5.44% were home visits and 13.11% were telephone consultations (Figure 6-2).

Figure 6-2 Annual number of primary care consultations, 2000-2010



Over the study period, the proportion of home consultations continued to rise significantly by an annual percentage change of 134.93% (95%CI: 39.90, 294.50, $p<0.001$) (Table 6-1). Similarly, consultations by telephone unremittingly escalated annually by 33.74% (95%CI: 32.50, 34.90 $p<0.001$). However, in the context of the absolute overall rates of consultations, these remained lower in comparison with surgery visits.

Table 6-1 Annual percent change in number of consultation rates, 2000-2010

Consultation-type	**Consultation rate (10^3)**		**APC (95%CI)**
	2000	**2010**	
GP face-to-face	17.18	213.79	29.11 (28.40-29.80)*
Home-visits	0.002[1]	14.28	134.93 (39.90-294.50)*
Telephone	1.95	34.43	33.74 (32.50-34.90)*
All-consultations	19.13	262.49	30.61 (29.70-31.50)*

[1]From 2002, APC: annual percent change, *p-value significant at ≤0.05

The median number of consultations per user per year varied with the specific consultation types (Table 6-2). While the median number of home visits and telephone consultations per user were both 2 per year (IQR: 1, 4 and IQR: 1, 5, respectively), the median number of face-to-face GP consultations per user per year was 9 (IQR: 4,15).

Table 6-2 Median number of consultations per long-term user per year

	Consultation type			
	GP	**Home**	**Telephone**	**All**
Median/year (IQR)	9 (4,15)	2 (1,4)	2 (1,5)	10 (5,18)

The duration of GP consultations in minutes also differed greatly between the start and end of the study period (Table 6-3). In 2000, the median duration of surgery visits per user was 4 minutes (IQR: 0,10) and in 2010 the median duration of GP appointments per user increased to 7 minutes (IQR: 2,13).

Table 6-3 Duration of GP consultations per user

	GP face-to-face consultations		
	All	**2000**	**2010**
Median, min (IQR)	7 (2,13)	4 (0,10)	7 (2,13)

Analysis of consultations by gender showed that female users had a median yearly consultation of 9 (IQR: 4, 15), whereas in males this was 8 (IQR: 4, 15) per year. Furthermore, the overall crude number of consultations made by female users grew significantly by 32.71% (95CI: 31.80, 33.70, p<0.001) per year (Table 6-4). Across age groups, although users aged ≥60 years contributed to the highest total number of consultations during the study period (n=630,600, 58.27%), greater annual changes in the consultation rate occurred in users aged 18-24 (38.44%, 95%CI: 34.30, 42.70, p<0.001) and 25-34 (36.06%, 95%CI: 33.70, 38.50 p<0.001).

Table 6-4 Annual percent change in number of consultations by age and gender, 2000-2010

Variable	**All, N (%)**	**APC (95%CI)**
Age, years		
18-24	7,398 (0.68)	38.44 (34.30-42.70)*
25-34	46,255 (4.27)	36.06 (33.70-38.50)*
35-39	52,256 (4.83)	30.83 (27.70-34.10)*
40-44	71,130 (6.57)	29.59 (27.10-32.10)*
45-49	78,216 (7.23)	30.63 (28.10-33.20)*
50-54	94,731 (8.75)	25.82 (24.90-26.80)*
55-59	101,689 (9.40)	28.18 (25.80-30.60)*
60-64	111,738 (10.32)	28.01 (27.20-28.80)*
65-69	108,374 (10.01)	32.79 (30.60-35.10)*
70-74	114,027 (10.54)	31.47(29.30-33.70)*
75-79	110,655 (10.22)	32.48 (31.30-33.70)*
>=80	185,806 (17.17)	32.67 (29.50-35.90)*
Gender		
Male	370,763 (34.26)	27.01 (25.80-28.20)*
Female	711,512 (65.74)	32.71 (31.80-33.70)*

*p-value significant at ≤0.05

Moreover, greater home visits and telephone consultation counts were observed among users aged ≥75 (55.65% and 30.49%, respectively).

6.5.2 Covariates linked to GP consultations

In a multivariate regression analysis and after accounting for users' age, gender, practice region, and long-term comorbidities, an increased number of GP visits per year was significantly influenced by: higher number of pain conditions at index date, smoking, obesity, high Townsend deprivation score and a diagnosis of depression and anxiety (Table 6-5). Co-medications with non-opioids, weak opioids, sedative-hypnotics and antidepressants were also associated with greater GP visitations per year.

Table 6-5 Adjusted odds ratios of factors linked to GP consultations per year

Variables	OR (95%CI)
Townsend deprivation	
Ref: 1-least deprived	
2	1.05 (0.93-1.18)
3	1.10 (0.98-1.24)
4	1.08 (0.96-1.22)
5-**most deprived**	1.24 (1.10-1.41)**
Smoking status Ref: non-smoker	
Smoker	1.12 (1.02-1.24)*
Ex-smoker	0.99 (0.90-1.10)
Obesity	1.75 (1.01-3.02)*
Pain conditions Ref: ≤1	
>1 condition	1.69 (1.53-1.88)***
Mental health illness	
Depression	1.41 (1.06-1.89)*
Anxiety	1.37 (1.00-1.87)*
Co-prescribed drugs	
NSAIDs	1.85 (1.73-1.97)***
Paracetamol	1.21 (1.14-1.29)***
Tramadol	1.77 (1.61-1.94)***
Weak opioids	1.60 (1.49-1.72)***
Antidepressants	1.59 (1.50-1.70)***
Benzodiazepines	1.36 (1.26-1.46)***
Non-benzodiazepines	1.55 (1.40-1.70)***

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$

6.5.3 Referrals to pain management specialists

Of the 26,703 long-term users in the study, 6.86% (n=1,832) had a referral to a pain management specialist. Frequency of users referred to the service grew slowly from initially 2.68% in 2000 to 5.97% in 2004, and from 6.62% in 2005 to 7.65% in 2010. Two thirds of all referred users were females (66.38%) and the average age of referred users was 55.24±16.17 (Table 6-6).

Table 6-6 Trend in referrals of long-term strong opioid users to specialist pain management

	Total users	**Referred users, N (%)**	**Non-referred users, N (%)**
Age (mean± SD,	65.31±17.07	55.24±16.17	66.05±16.90
Gender			
Male	9,348	616 (33.62)	8,732 (35.11)
Female	17,355	1,216 (66.38)	16,139 (64.89)
Year			
2000	485	13 (2.68)	472 (97.32)
2001	594	15 (2.53)	579 (97.47)
2002	727	13 (1.79)	714 (98.21)
2003	804	34 (4.23)	770 (95.77)
2004	905	54 (5.97)	851 (94.03)
2005	1,164	77 (6.62)	1,087 (93.38)
2006	1,574	96 (6.10)	1,478 (93.90)
2007	2,124	159 (7.49)	1,965 (92.51)
2008	2,630	176 (6.69)	2,454 (93.31)
2009	3,174	237 (7.47)	2,937 (92.53)
2010	12,522	958 (7.65)	11,564 (92.35)

The average (OMED) dose used by referred users was almost double that of non-referred users, and the duration of drug-supply was 20.02% higher in referred users (Table 6-7).

Table 6-7 Average annual (OMED) dose per user per day and days' supply of referred users

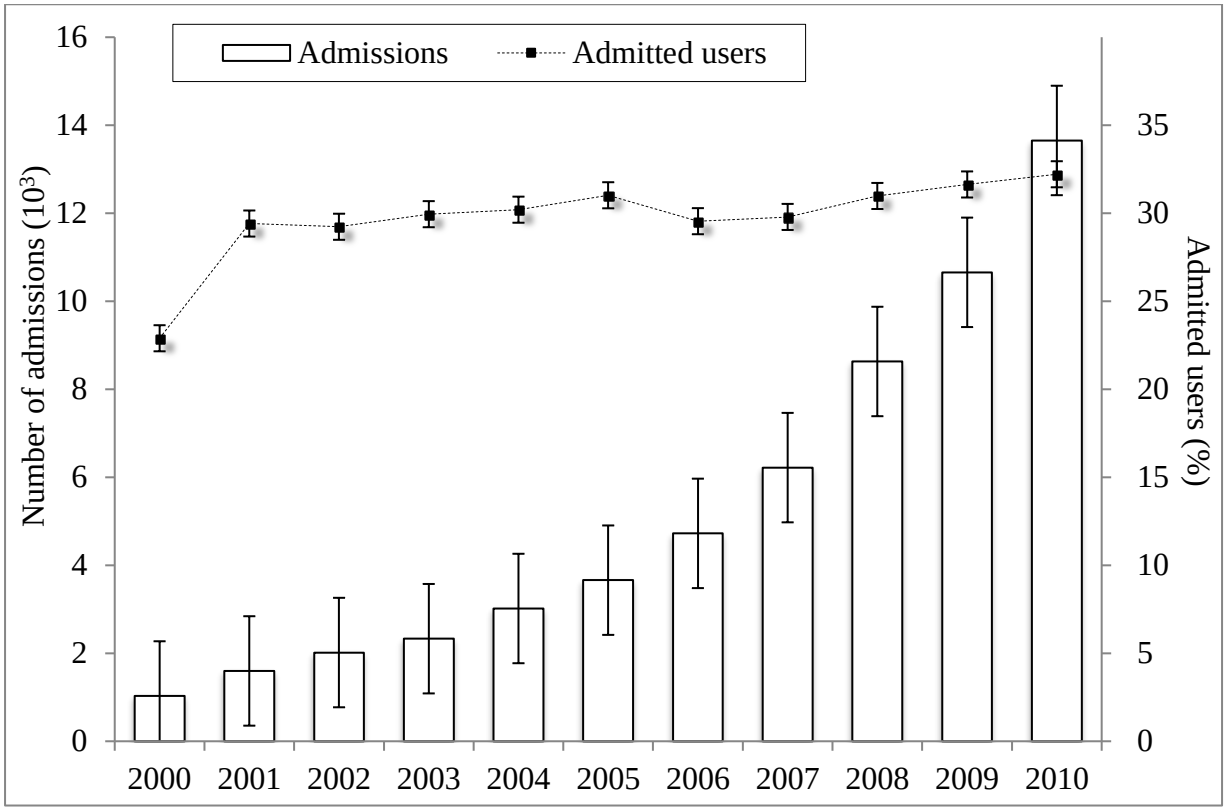
Type of user	**N (%)**	**Mean daily dose/year, mg±SD**	**Mean days' supply±SD**
Not referred	24,871 (93.14)	80.94±89.16	215.80±90.94
Referred users	1,832 (6.86)	110.16±116.65	259.01±92.32

6.5.4 Hospitalisation: in-patient admissions

During the 11 years of follow-up, 41.41% (n=11,059) of long-term users had one or more in-patient hospital admissions recorded after the index date. This accounted for a total of 57,537 in-patient admissions and an average of 1.93±1.37 admissions per user per year.

Figure 6-3 points out the trend of in-patient admissions over time. The frequency of admissions continued to increase each year by an annual percentage change of 28.16% (95%CI: 26.40, 29.90, p<0.001) from n=1,029 admissions in 2000 to n=13,654 in 2010. Correspondingly, the prevalence of long-term users admitted to hospital per year grew from 22.90% in 2000 to 32.21% in 2010.

Figure 6-3 Annual trend in-patient hospital admissions, 2000-2010



It was noted that the majority of strong opioid users who had a record of hospital admission had a total of 1-3 (60.33%, n=6,672) admissions over the 11 years. However, more than a third (39.67%, n=4,387) of users had 4 or more admissions during the course of the study (Table 6-8).

Table 6-8 Number of admissions made by the long-term users over the 11-year follow up

Total number of admissions	**Number of users (%)**
1	3,077 (27.82)
2	2,144 (19.39)
3	1,451 (13.12)
4	951 (8.60)
5	773 (6.99)
6	545 (4.93)
7	375 (3.39)
8	276 (2.50)
9	232 (2.10)
≥10	1,235 (11.16)

Demographic characteristics of users with one or more admissions during follow-up are shown in Table 6-9. Admitted users were typically females (63.69%), had an average age of 65.18±16.81 years and tended to live in North West (18.70%) of England. More than half of the admitted users had a deprivation quintile of ≥2, with 22.15%, 21.89% and 21.99% having quintiles of 2, 3 and 4, respectively.

The main distinctive differences in the characteristics of long-term users who had one or more admissions in the 11 years compared to those without (58.59%, n=15,644) were in clinical diagnostic traits.

Higher proportions of admitted users had a greater count of pain conditions and comorbidities than their equivalent counterparts of users without admissions. Forty-five (n=4,981) percent of

users with one or more admissions had one or more pain conditions diagnosed up to 6 months prior to the index date, and 18.29% (n=2,023) of them had one or more long-term comorbidities, including psychiatric disorders.

Table 6-9 Characteristics of in-patient admitted long-term users versus non-admitted users

Demographic	**Admitted, N (%)**	**Non- admitted N (%)**	**Test (df)**	***P*-value**
Mean age±SD	65.18±16.81	65.39±17.25	t(26,701)=1.00	0.32
Rank of age				
≤40 years	1,073 (9.70)	1,435 (9.17)		
41-50 years	1,300 (11.76)	2,056 (13.14)		
51-65 years	2,783 (25.17)	3,970 (25.38)		
66-80 years	3,596 (32.52)	4,610 (29.47)		
≥81 years	2,307 (20.86)	3,573 (22.84)	$X^2(4)=43.08$	<0.001
Gender				
Female	7,044 (63.69)	10,311 (65.91)		
Male	4,015 (36.31)	5,333 (34.09)	$X^2(1)=13.98$	<0.001
Region				
North East	417 (3.77)	209 (1.34)		
North West	2,068 (18.70)	1,478 (9.45)		
Yorkshire & Humber	575 (5.20)	517 (3.30)		
East Midlands	329 (2.97)	507 (3.24)		
West Midlands	1,377 (12.45)	1,054 (6.74)		
East of England	1,303 (11.78)	960 (6.14)		
South West	1,532 (13.85)	990 (6.33)		
South Central	1,203 (10.88)	1,264 (8.08)		
London	979 (8.85)	789 (5.04)		
South East Coast	1,276 (11.54)	1,232 (7.88)	$X^2(9)=233.45$	<0.001
Townsend score				
1 least deprived	1,992 (18.01)	3,642 (23.28)		
2	2,450 (22.15)	3,787 (24.21)		
3	2,421 (21.89)	3,397 (21.71)		
4	2,432 (21.99)	2,992 (19.13)		
5 most deprived	1,764 (15.95)	1,826 (11.67)	$X^2(4)=46.25$	<0.001
Smoking status				
Non-smoker	4,176 (37.76)	6,021 (38.49)		
Smoker	2,985 (26.99)	4,274 (27.32)		
Ex-smoker	3,898 (35.25)	5,349 (34.19)	$X^2(2)=5.39$	0.07
Pain condition				
≥1	4,981 (45.04)	6,408 (40.96)	$X^2(1)=44.07$	<0.001
Comorbidities				
≥1	2,023 (18.29)	2,372 (15.16)	$X^2(1)=46.18$	<0.001

p-value significant at ≤0.05

6.5.5 Covariates associated with in-patient hospitalisation

Multivariate generalized estimating equation model was used to analyse factors that were linked to in-patient hospitalisation of long-term strong opioid users during follow-up (Table 6-10). In the adjusted model, factors such as an age >50 years, specifically 65-75 years (aRR: 1.26; 95%CI 1.14, 1.39), and a greater yearly number of GP visits (>3 visits/year) were associated with increased likelihood of all-cause in-patient hospitalisation. A high Townsend score was associated with a 69% (95%CI: 1.53, 1.88) increased odds of hospitalisation in the unadjusted model, but this was no longer significant in the adjusted analysis.

In addition, chronic morbidities such as osteoporosis (aRR: 1.20; 95%CI: 1.01, 1.42), diabetes (aRR: 1.30; 95%CI 1.07, 1.59), asthma (aRR: 1.28; 95%CI: 1.02, 1.61), COPD (aRR: 1.28; 95% CI: 1.06, 1.55), heart failure (aRR: 1.52; 95%CI: 1.18, 1.95) and coronary heart disease (aRR: 1.57, 95%CI: 1.29, 1.91) were all significantly linked to a greater odds of hospitalisation in the unadjusted model. On the other hand, only coronary heart disease (aRR: 1.41, 95%CI: 1.10, 1.81) remained significantly linked to the risk of in-patient admission in the adjusted model (Table 6-10).

Also, in the final adjusted model, a high daily dose use (>120mg/day) of strong opioids (37%) and co-prescriptions with psychoactive drugs such as antidepressants, benzodiazepines, and non-benzodiazepines were linked to a marked increase (7%, 17%, 15% respectively) in the odds of hospitalisation compared to the use of lower daily (OMED) doses and no prescriptions with the specified drugs (Table 6-10).

Table 6-10 Univariate and multivariate analysis of covariates linked to in-patient admissions

Variables (Reference Group)	Unadjusted Risk Ratio (95%CI)	Adjusted Risk Ratio (95%CI)
Age (<50 years)		
50-64	1.00 (0.93-1.08)	1.09 (1.00-1.19)*
65-74	1.12 (1.04-1.21)**	1.26 (1.14-1.39)***
≥75	1.01 (0.94-1.08)	1.11 (1.01-1.22)*
Gender (Male)		
Females	0.91 (0.86-0.95)***	0.89 (0.83-0.94)***
Region (North East)		
North West	0.70 (0.59-0.84)***	0.69 (0.58-0.83)***
Yorkshire and Humber	0.56 (0.45-0.68)***	0.53 (0.43-0.66)***
East Midlands	0.33 (0.26-0.40)***	0.31 (0.25-0.39)***
West Midlands	0.65 (0.54-0.79)***	0.64 (0.53-0.77)***
East of England	0.68 (0.56-0.82)***	0.68 (0.56-0.82)***
South West	0.78 (0.65-0.93)**	0.77 (0.63-0.93)**
South Central	0.48 (0.40-0.57)***	0.46 (0.38-0.56)***
London	0.62 (0.51-0.75)***	0.65 (0.53-0.79)***
South East Coast	0.52 (0.43-0.62)***	0.52 (0.43-0.63)***
GP visits (1-3 visits/year)		
4-7 visits/year	1.22 (1.13-1.32)***	1.29 (1.18-1.41)***
8-11 visits/year	1.40 (1.29-1.53)***	1.45 (1.32-1.60)***
≥12 visits/year	1.88 (1.75-2.01)***	1.88 (1.72-2.04)***
Townsend score (1-least deprived)		
2	1.15 (1.03-1.27)**	1.01 (0.91-1.12)
3	1.29 (1.18-1.40)***	1.01 (0.91-1.12)
4	1.42 (1.30-1.56)***	1.01 (0.91-1.13)
5-most deprivation	1.69 (1.53-1.88)***	1.04 (0.91-1.17)
Smoking (smoker)		
Non-smoker	0.99 (0.90-1.09)	0.99 (0.87-1.11)
Ex-smoker	1.05 (0.96-1.14)	1.00 (0.90-1.12)
Medical comorbidity		
Osteoporosis	1.20 (1.01-1.42)*	1.17 (0.96-1.44)
Diabetes	1.30 (1.07-1.59)**	1.15 (0.90-1.46)
Asthma	1.28 (1.02-1.61)*	1.04 (0.79-1.37)
COPD	1.28 (1.06-1.55)**	1.11 (0.89-1.40)
Heart failure	1.52 (1.18-1.95)**	1.17 (0.87-1.58)
Coronary heart disease	1.57 (1.29-1.91)***	1.41 (1.10-1.81)**
Psychiatric comorbidity		
Depression	1.36 (1.12-1.65)**	1.20 (0.93-1.55)
Anxiety	1.14 (0.91-1.43)*	1.04 (0.77-1.40)
OMED (≤120mg/day)		
>120mg/day	1.35 (1.26-1.44)***	1.37 (1.27-1.49)***

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$

(Continued) Table 6-10 Univariate and multivariate analysis of covariates linked to in-patient admissions

Variables	Unadjusted Risk Ratio (95%CI)	Adjusted Risk Ratio (95%CI)
Co-prescribed drugs		
Weak Opioids	0.86 (0.81-0.91)***	1.05 (0.98-1.13)
Benzodiazepines	1.01 (0.93-1.07)	1.17 (1.09-1.26)***
Non-benzodiazepine	1.16 (1.08-1.25)***	1.15 (1.05-1.27)**
Antidepressants	1.20 (1.14-1.26)***	1.07 (1.00-1.14)*
Antipsychotics	1.14 (1.06-1.23)***	1.03 (0.95-1.13)
Antiepileptic	1.16 (1.09-1.23)***	1.15 (1.07-1.24)***

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$

6.5.6 Prescribing patterns of hospital admitted strong opioid users

Users with a record of one or more admissions during follow-up were found to have a greater exposure to strong opioids in terms of oral morphine equivalent daily dose and daily drug supply compared to long-term users without a record of in-patient hospitalisation (Table 6-11). Admitted users had a 17.86% higher average oral morphine equivalent daily dose of 91.03±99.97 mg per user per year, and their average days' supply was 223.86±91.85 days per user per year.

Table 6-11 Annual (OMED) dose per user per day and days' supply of admitted users

Type of user	Users, n (%)	Mean daily dose (OMED)/year, mg (SD)	Mean days' supply/year (SD)
Not admitted	15,644 (58.59)	77.23±84.73	215.16±91.40
Admitted	11,059 (41.41)	91.03±99.97	223.86±91.85

Almost a quarter of all admitted users (23.78%, n=2,630) had an annual average daily dose defined as high dose use in current national recommendations (greater than 120mg/day). It was noted that the high dose users had the longest average days' supply of 248.33±92.95 days per user per year.

6.5.7 Primary cause of admissions and re-admissions

The main causes of in-patient hospitalisation are summarized in Table 6-12. The most frequently occurring reason for the admissions of the study population, according to the WHO International Classification of Diseases, were disorders of the musculoskeletal system (18.35%), which included arthritis, low back pain, and sciatica. This was followed by admissions related to: neoplasm diagnosis (13.73%); diseases of the genitourinary system (11.18%), such as renal failure; dysfunction of the bladder; and circulatory system disorders (10.66%), such as congestive heart failure and cerebral infraction. Two other categories each that resulted in 9.55% and 5.38% of all in-patient hospitalisation in the users were: digestive and respiratory disorders respectively.

Table 6-12 Primary cause of long-term strong opioid users' in-patient admissions

Primary causes	**Total number of admissions**	
Cause as defined by ICD-10	**N (%)**	**%**
Diseases of the musculoskeletal system and connective tissue	10,558	18.35
Neoplasms	7,897	13.73
Diseases of the genitourinary system	6,435	11.18
Symptoms, signs and abnormal clinical and laboratory findings	6,132	10.66
Diseases of the circulatory system	5,877	10.21
Diseases of the digestive system	5,493	9.55
Injury and certain other consequences of external causes	3,098	5.38
Diseases of the respiratory system	3,093	5.38
Factors influencing health status and contact with health services	1,501	2.61
Diseases of the skin and subcutaneous tissue	1,417	2.46
Diseases of the eye and adnexa	1,391	2.42
Diseases of the blood and certain disorders involving the immune mechanism	1,272	2.21
Diseases of the nervous system	1,216	2.11
Others	2,157	3.76

Note: other causes: (a) endocrine, nutritional and metabolic diseases, (b) mental and behavioural disorders, (c) diseases of the ear and mastoid process, (d) certain infectious and parasitic diseases (e) congenital malformations and puerperium related morbidity

When causes of admissions related to musculoskeletal conditions were examined further, it was found that low back pain was the main reason for in-patient admissions (16.35%), followed by dorsalgia unspecified (5.03%), pain in the joint (4.61%) and rheumatoid arthritis unspecified (4.21%) (Table 6-13). These conditions combined resulted in almost a third (30.20%) of all musculoskeletal-related hospital admissions during the observation years. Unspecified osteoarthritis of the knee or joint (termed Gonarthrosis unspecified and Coxarthrosis unspecified) were the next most common musculoskeletal-related primary causes of hospitalisation, and were responsible for 3.76% and 3.71% of admissions, respectively.

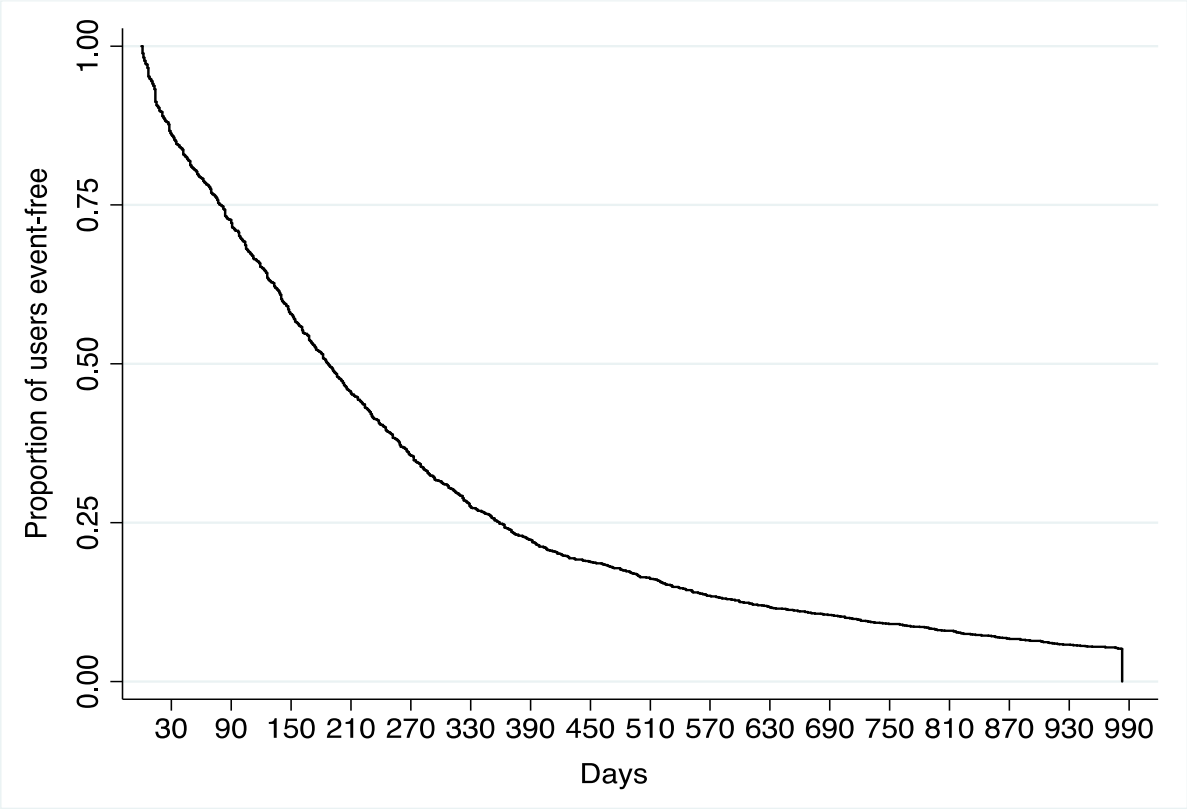
Table 6-13 Type of musculoskeletal related primary cause of in-patient admissions

Primary causes	**Total number of admissions**	
Diseases of the musculoskeletal system	**N**	**%**
Low back pain	1,726	16.35
Dorsalgia, unspecified	531	5.03
Pain in joint	487	4.61
Rheumatoid arthritis unspecified	444	4.21
Gonarthrosis, unspecified	397	3.76
Coxarthrosis, unspecified	392	3.71
Lumbar and other intervertebral disc disorders	384	3.64
Pain in limb	370	3.50
Others	5,827	55.19

Musculoskeletal pain was also the main reason for re-admissions, and readmissions occurred in 26.02% (n=2,077) of long-term users who had 2 or more records of all-cause re-admissions (n=7,982). Of the 2,077 long-term users with MSK pain related re-admissions, 44.87% (n=932) were re-admitted once, 21.09% (n=438) were readmitted twice, 10.78% (n=224) were re-admitted three times and 23.25% (n=483) were re-admitted four or more times over the length of the study period.

Kaplain Meier plot was used to graphically present the proportion of long-term users not re-admitted for an MSK pain-related cause from the time of the first in-patient discharge to the time of first re-admission (Figure 6-4). This demonstrated that approximately one-fourth (27.21%) of long-term users had a re-admission that was related to MSK pain within 90 days of the initial discharge, a fifth (20.03%) had a re-admission within 180 days, and 25.90% of users had a re-admission a year or more following discharge from the initial admission.

Figure 6-4 Kaplan-Meier plot of the proportion of long-term users with MSK-related re-admission over time



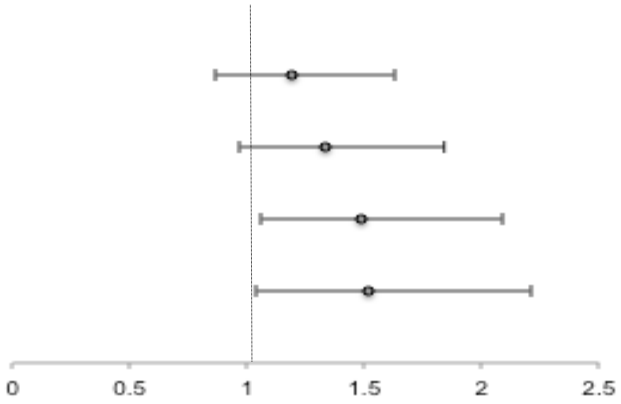
	Time to re-admission (days)					
Users	**1-30**	**31-90**	**91-180**	**181-270**	**271-365**	**>365**
N (%)	283 (13.63)	282 (13.58)	416 (20.03)	327 (15.74)	231 (11.12)	538 (25.90)

In multivariate-adjusted analysis, there was a significant relationship between high dose use and the risk of MSK pain-related re-admission. Recipients of a daily dose of strong opioids of

100-199mg/day OMED had a 49% increased risk of being re-admitted for a musculoskeletal-related condition (Figure 6-5). The likelihood of the association was further attenuated with increases in dosage thereafter, with greater risks of readmissions with a use of ≥200mg/day (aRR: 1.52, 95%CI: 1.04, 2.21). Contrariwise, a (OMED) dose less than 99mg/day and less than 49mg/day was not significantly linked to MSK-related re-admission.

Figure 6-5 Multivariate analysis of the influence of (OMED) dose per day on the risk of MSK pain-related re-admission

Variables	**aRR (95%CI)**
(**Reference:** 1-19mg/day)	
20-49mg	1.19 (0.86-1.63)
50-99mg	1.33 (0.97-1.84)
100-199mg	1.49 (1.06-2.09)*
≥200mg	1.52 (1.04-2.21)*



*p-value significance at ≤0.05, adjusted for socio-demographic factors and clinical conditions

6.5.7.1 Length of stay for all-cause and MSK pain related admissions

The overall median length of in-patient stay for all-cause admissions was 2 days (IQR: 1, 7). The median duration of hospital stay was 3 days (IQR: 1, 10) for users aged between 75-84, and longer amongst users aged ≥85 with a median of 5 days (IQR: 1, 14) stay. For users with a primary diagnosis of musculoskeletal-related disorders, length of stay was 2 days (1, 7) for users aged ≥65 and 3 days (IQR: 1, 15) for users aged >85.

6.6 Discussion

6.6.1 Main findings

This study's main aim was to examine primary and secondary healthcare use of non-cancer pain patients prescribed strong opioids long-term. Despite the growth in the crude number of GP consultations over time, the overall number of hospital in-patient admissions made by the long-term users continued to increase annually by 28.16% between 2000 and 2010. By the end of the study time, one third of long-term users were found to have had one or more in-patient admissions.

Musculoskeletal conditions were the main reason for hospitalisation and within musculoskeletal pain conditions, low back pain, spine pain (dorsalgia), and arthritis was amongst the most common causes for the admissions. For a large proportion of users (27.21%) re-admission for musculoskeletal-related disorders occurred within 90-days following the first hospital discharge.

Duration of hospital stay differed by long-term users' age. The duration was found to be longest in users between 75-84 years of age and in those aged >85 years, with a median hospital stay of 3 days and 5 days respectively.

Compared to users without any records of admissions, a greater proportions of long-term users admitted to hospital had one or more long-term comorbidities up to 6 months prior to the index date. Furthermore, users with one or more admissions were found to be prescribed a greater average oral morphine equivalent daily dose and longer number of days of drug supply compared to users without a record of in-patient admission. A strong correlation was found between high (OMED) daily dose use of strong opioids and an increased risk of (in-patient)

hospitalisation after adjusting for age, gender, region, pain conditions and co-morbidities. In addition, more GP visits and co-prescriptions of psychoactive medications were also significantly associated with greater odds of in-patient admissions.

6.6.2 Primary healthcare use

One of the most widely acknowledged and commonly adopted frameworks for understanding the utilisation of healthcare has been Andersen's healthcare service use model. This conceptual framework defines categories of possible explanatory factors of healthcare use, which enables a way of conceptualizing differences in the rates and consumption of resource use [389, 390]. In this model, Andersen RM et al. (1995) explains that the use of healthcare services can be described through three main elements, which include: predisposing factors, enabling factors and need factors. Need factors, which in most cases explain a continued service use, include the health status of individuals, which contributes to the need to seek healthcare. Enabling factors include factors that may affect patients' ability to access healthcare such as access to regular service care, health insurance and income. Lastly, predisposing factors, such as socio-demographic and health beliefs, provide an additional explanation to patterns and differences in healthcare use.

In the current study of long-term strong opioid users, primary care consultations have been found to differ with predisposing factors such as age and gender. Female users had a slightly higher use of GP consultations per year than males, and they significantly contributed to the overall crude count of all types of consultations (GP, home visits and telephone) over the 11 years. Furthermore, the total number of GP consultations increased with age. The rates of home visits and telephone consultations were mostly utilised by elderly users aged ≥75 years, which is likely to reflect adaptation in the delivery of healthcare in this user-group. Socioeconomic

status measured as Townsend deprivation scores was also found to be a significant predisposing factor for GP visits. Users with the highest level of (score of 5) deprivation were 24% more likely to have more GP visits per year.

It is known from previous studies that socioeconomic disadvantage influences the susceptibility of an array of pain conditions. Socially disadvantaged individuals tend to report more chronic pain disorders with higher pain intensity, which could be positively correlated with primary healthcare use and medication use [4, 391-394].

It has also been reported that self-management and coping with chronic pain are influenced by patients' socioeconomic circumstances. In particular, Roth and Geisser (2002) examined a cohort of chronic pain patients attending a pain clinic and observed that coping strategies, perception of pain and the seeking of care differed by patients' socioeconomic status [395]. In the study, socioeconomically disadvantaged subjects were more inclined to have a maladaptive pain coping mechanism, including catastrophizing behaviour, and were more likely to believe and report their pain to need a medical solution compared to subjects with higher socioeconomic status.

Moreover, the number of pain conditions recorded at index date amongst the study population, which was used as an indicator of healthcare need and a plausible need-based factor, was found to be linked to the rate of GP visits per year. The findings suggested that, after controlling for age, gender, region and long-term comorbidities, users with heavier burden of pain conditions prior to the index date had 69% higher odds of a greater number of GP appointments per year. This finding is likely to have important implications since in the UK, long-term morbidity has been known to relate to both GP workload and costs [396].

There are however other possible factors such as the number of healthcare personnel available, distribution of health service facilities, and management factors such as waiting times, which could have further influenced the utilisation of GP consultations. The factors were not accounted for in the study due to the unavailability or limited feasibility of their collection from the records in the database.

6.6.3 Secondary healthcare use

The majority (93.14%) of long-term users had their pain managed in primary care with only 6.86% of users ever referred to multidisciplinary specialist care during the 11 years. As discussed in chapter 2 (page 25), multidisciplinary pain management interventions have only recently received attention and as such, very few studies exist to compare the current results. Importantly, there is a dearth of research exploring factors influencing primary care practitioners' patient-referrals to pain clinics, and it was beyond the scope of the research to examine possible motivations and selection procedures utilised by physicians for referrals to specialist care.

However, a growing body of international research has shown promising outcomes from the incorporation of a team-based medical care model to pain management (i.e. physical, occupational, psychological therapies and interventions) to address the many clinical facets of patients' pain [397-400]. It has also been suggested that specialist pain management interventions may minimises the sole burden of primary care physicians' care of complex chronic pain patients in clinical practice [401]. In the current study, the fact that a large proportion of patients were managed exclusively in primary care over the 11 years imply that specialist pain care was not available for the majority of the patients, which suggests an under-utilization of such specialist care.

This could be explained, in part, by the considerable shortage in the availability and accessibility of pain services across the UK. The National Pain Audit and a workforce planning analysis undertaken by the Faculty of Pain Medicine (FPM) reported a wide variation in the availability of pain specialists per capita, and highlighted that there were fewer pain doctors per capita, particularly in England and Wales (0.8 specialist per 100,000 population) compared to Scotland (1.0 per 100,000 population) and Northern Ireland (0.9 per 100,000 population) [356]. Moreover, in the year 2000 the Department of Health's Clinical Services Advisory Group reviewed the provision of specialist pain services in the UK and reported that 1 in 4 of chronic pain patients had a 22-week waiting time for a referral to pain management clinics, which exceeded the advised NHS England standard of a maximum of 18-weeks waiting time for referrals to treatment [91].

According to national recommendations, specialised pain management should be sought for complex patients such as those with multiple comorbidities including psychiatric morbidities, and those unresponsive to analgesic treatment, including patients who need high opioid doses [47-49, 402]. Examination of the study populations' opioid utilisation pattern, which was detailed in the previous chapter, showed that approximately 1 in 4 of long-term users were using high daily doses exceeding 120mg morphine equivalent per daily, and given the clinical characteristics of the long-term users, the expected impression of the current results was that the referral rate would have been greater than 25%. Invariably, the low referral rates and the frequent GP consultations may provide an account for the increase in the use of strong opioids over prolonged periods of time, including the use of higher daily doses observed in the study.

Low referral rates to pain management services have previously been reported in a UK study by Stannard C et al. (2003). The study carried out a quantitative survey using questionnaires

and qualitative face-to face interviews of 569 GPs, from November 2001 to January 2002, about their management of CNCP in primary care [403]. The study reported that although 91% of GPs thought that specialist pain clinics were valuable in managing patients' pain, only 14% of collective patients had been referred to the service. The low referral count was considered to be due to barriers such as long NHS-waiting time, which was reported to have been between (medium) 4 to 5 months. Unlike the current study, Stannard's study examined referrals for a general non-cancer pain population in primary care without accounting for analgesic use patterns nor clinical traits, which may explain differences in the results observed in relation to the current study.

One of the main findings from the current study was that in-patient hospital admissions were common amongst the study population and this continued to gradually increase over time during the study follow up. Furthermore, a large proportion of patients (45.35%) experienced re-admissions. Accordingly, this confirms a continued demand for hospital care by the study sample, which lends credence in viewing the study participants as a vulnerable group of patients with general susceptibility to health problems and who may require close and early attention.

The avoidance of high use of hospital care is a priority for national policy-makers due to the perpetual costs this incurs to the healthcare system; but also, rates of admissions are often used as a marker of quality of care within the NHS, and re-admissions indicate suboptimal care [404-406]. Thus, gaining a detailed insight into the context of the characteristics in terms of demographics, clinical and medical traits of patients who are likely to be admitted and re-admitted to hospital can inform clinical evidence-based decision-making about the type and extent of care, including targeted interventions that will be needed and for whom it is needed.

Clinical and administrative details of inpatient admissions at NHS hospitals in England are routinely collected by the Hospital Episode Statistics service, and this has been utilised in previous studies to examine all-cause hospital attendances (inpatient admissions and outpatient visits) of the general population in England. Previous national reports have reported common frequent causes of admissions to be related to ailments of the cardiovascular system (ICD chapter I), respiratory system (ICD-chapter J), digestive system (ICD chapter K), and signs and symptoms (ICD chapter R) [407-409]. In the current study, unexpectedly, musculoskeletal pain disorders were the most common reason for hospital admissions. This was startling due to the study populations' long-term therapeutic management with strong opioids. It was thus likely that patients' pain disorder(s), which most likely prompted the use of strong opioids, may have been poorly responsive or inadequately addressed by the therapeutic management, thus contributing to a need of hospital care.

This assumption was further strengthened by the results, which showed that the risk of musculoskeletal pain-related admissions was correspondingly the main reason for re-admissions. One in four users had a re-admission within 90 days of discharge of the initial admission and given that the average annual length of strong opioid use amongst hospital admitted users was 223.86±91.85 days, this suggests that the prescribed drug-therapy would have likely to have been used beyond the length of time between admission and re-admission for a large proportion of users.

Moreover, long-term users who received higher strong opioid doses were at an increased risk of MSK-related re-admission relative to users prescribed lower doses, even after controlling for demographic and clinical factors. Although the risk of re-admissions was highest (52%) in

patients prescribed a daily dose of ≥200mg/day, the risk was also found to be (almost two-fold) higher in long-term users receiving strong opioids doses at ≥100mg/day.

This suggested that an incremental increase in OMED dose, starting at a dose of >99mg/day, did not seem to offer an inverse effect that resulted in a reduction in the risk of hospitalisation. This prompts the need of reviews, monitoring and vigilance, particularly at medium to high daily doses. Currently, research has suggested that a significant improvement in the management of musculoskeletal disorders is needed, including a need for an enhanced understanding of the multidimensional nature of the painful disorders and the relationship with analgesic treatment, response and outcomes [410-412].

The upward trend in (all-cause) hospital admission of long-term strong opioid users over time was in line with trends in several international studies. Liang Y et al. (2015) used a large US health-insurance claims database to trace non-cancer pain patients prescribed long-term opioids and examined their hospital utilisation [380]. Trends were examined at 6-month intervals over 3 years (January 2009 to July 2012) and, strikingly, the study found an all-cause hospitalisation rate of 1120 per 10,000 person-year amongst the cohort, which translated to an average rate of 12% of users hospitalised each year. In addition, the study found an association between the likelihood of admissions and daily dose, with <20mg, 20-49mg, 50-99mg and ≥100mg associated with a 33%, 84%, 96%, and a two-fold increase in hospitalisation, respectively.
Meanwhile, Kern and colleagues (2015) conducted a retrospective follow-up study of adult non-cancer pain patients using opioids (using US medical claims data) and noticed a rise in in-patient admissions from 0.25 admissions to 0.77 per patient-year. Patients indexed on strong opioid use continued to have greater rates of hospitalization compared to patients who received weak opioids. Additionally, users of opioids long-term (≥6 months) had longer hospital stays

(median in-patient length of stay 5 days) than their counterparts who used opioids over an intermediate-length of time (30 to 182 days) (median=3 days) [381]. In particular, patients prescribed strong opioids continued to have higher rates of hospitalisation during the 4-year study follow-up relative to those using weak opioids.

A few other studies have examined outcomes following hospital discharge of chronic pain patients who used long-term opioids prior to hospital care and reported a worsening of long-term health-outcomes [413-416]. For example, Zywiel MG et al. (2011) followed chronic opioid users before and after their total knee arthroplasty and compared pain management, rehabilitation and clinical outcomes to a matched group who had not used opioids. The study reported a slower recovery, experience of greater stiffness, pain and further complications that required additional secondary care, including referrals to pain management care in patients who had used opioids long-term prior to hospital care [415]. The study concluded that an earlier referral to orthopaedic services prior to long-term opioid use would need to be considered.

While the clinical characteristics of patients initiated with long-term opioids have been examined in several previous studies [339, 417-419], fewer studies have detailed the traits of long-term opioid users who have been hospitalised, and the possible explanatory factors associated with the event. In the current study, a number of patient-level factors were identified as contributors of the risk of hospital in-patient admissions. An advanced age was related to a greater likelihood of admission and hospital stay. A likely interpretation of this is that an older age is known to be associated with age-related physiological changes to several organ systems that predisposes this group to a wide range of health conditions, which necessitates health service care [420]. Indeed, analysis in the previous chapter (chapter 4 page: 125, 126) revealed that the disease burden (number of pain conditions and long-term co-morbidities) increased

with age, and MSK pain disorders were specifically common in this sub-group. This is likely to have been due to age-related alterations in the musculoskeletal system (a reduction in lean mass and bone) that are part of the multifactorial etiology of many MSK pain conditions [421].

In addition, hospitalised patients were noted to have higher levels of multiple chronic conditions (pain and QOF conditions) than non-admitted patients, making them clinically and medically complex patients to treat and manage. More specifically, long-term morbidities such as diabetes, osteoporosis, COPD, and heart failure displayed an individual strong link to the risk of admission. This finding does not negate the position of the primary cause of admissions, but it accentuates the importance of patients' other morbidities of influence.

Published literature to date have postulated that the presence of multiple chronic morbidities poses a perpetual threat to patient's overall well-being, and that the joint presence of chronic pain and general long-term morbidities can have a negative impact on patients' health and, eventually, the care-seeking behaviour, more so than the existence of either conditions alone [421]. In particular, Duffield SJ et al. (2017) highlighted that musculoskeletal disorders tended to often co-occur with certain long-term morbidities (e.g. cardiovascular conditions, osteoporosis) due to shared aetiology and shared risk factors, which tended to interact and contribute to an overall pervasive ability to maintain health [421].

However, in the current study, the conditions displayed little significance in influencing the risk of admissions in the multivariate adjusted analysis, and this could possibly have been due to the confounding effect of other variables in the analysis. Conversely, lower socio-economic status, and psychological distress, such as depression, was both independently associated with the risk of hospitalisation but were insignificant in the multivariable adjusted model. This

invites a more speculative explanation such as the likely strength of the interaction of "other" variables in the adjusted model.

The frequency of GP consultations per year remained a strong influencer in the univariate and multivariate analysis. The link between the number of GP consultation per year and the risk of hospitalisation was unanticipated mainly due to a natural belief that an increased physician-encounter would provide opportunities for patient monitoring and treatment evaluation. However, greater GP consultation could have invariably been related to long-term strong opioid prescription use, increased dose use, and the co-prescribing of psychoactive medication, of which the two latter variables were independently related to the risk of hospitalisation.

6.6.4 Strengths and limitations

This study, to the best of our knowledge, is the first population-based study to have evaluated primary healthcare use and in-patient hospital admissions of non-cancer pain patients managed therapeutically with long-term strong opioids. The outcomes were measured longitudinally over a long follow-up period, which is likely to have been advantageous in assessing changes over time. Furthermore, the use of a generalized estimating equation to predict factors associated with the outcomes was able to overcome limitations that are often associated with longitudinally measured datasets, such as correlations between and within individual patients' measurements and heterogeneity.

However, there are a number of limitations of the study that need to be acknowledged. Firstly, CPRDs' linkage to HES is currently available for English practices only. Thus, as a consequence, a subset of long-term users who were registered with practices in the other

countries of the UK (Northern Ireland, Scotland and Wales) were not included in the analysis, and the result is only a reflection of admissions made within England.

Secondly, although users' strong opioid exposure was repeatedly measured in each year during follow-up, exposure, specifically just before and after each admission and discharge, was not identified. This limited the extent of commentary that could be made on users' strong opioid use around the hospitalisation event(s). Furthermore, although the study attempted to incorporate a range of patient factors in the multivariate analysis, it is possible that other unmeasured confounders could have further affected users' primary and secondary healthcare use such as organisational factors, post-discharge care etc.

It should also be noted that although a cut-point of GP-visits per year of 3 in the multivariate analysis allowed the relationship of lower ranges of GP visits per year to the risk of hospitilsation to be explored, however, the disimilar cut-point value from the the median meant that a direct comparison of findings with a potential median category was not feasible.

Lastly, the relationship between patient-factors and study populations' primary and secondary healthcare use cannot be assumed to be causal. Nevertheless, the current study (which was able to adjust for conditions, including mental health, that are known to increase risk of hospitalisation) sheds light on the contributions of several important variables, which draws attention to their existence and influence on the healthcare experience of patients prescribed the potent drugs long-term.

6.6.5 Conclusions

Primary care consultations by long-term users were found to have grown substantially in the 11 years of the study period. Meanwhile, during this time and following the index date, two-fifths of the users had one or more in-patient hospitalisation, and musculoskeletal-related conditions were the main reason for admissions. Greater GP consultations, co-prescriptions with psychoactive medications and high opioid doses were significantly associated with increased odds of hospital admission. Recognition of these covariates and the general traits of patients (prescribed strong opioid long-term) who had one or more hospital admissions would be useful in informing risk prevention-strategies and intervention.

Chapter 7. General discussion and implications of findings

The chapter will initially discuss key results that emerged from the research studies in the thesis followed by an outline of the implications of the findings to policy and practice. Furthermore, the chapter discusses the overall strengths and shortcomings of the work before suggesting avenues for future research based on the reflection of the results.

7.1 Summary of key findings

As the management of chronic non-cancer pain continues to gain greater attention in the literature, the most debated matter remains to be the use of opioids in chronic non-cancer pain. CNCP refers to a constitution of a wide array of peripheral and central conditions and while some conditions are characterized by a degree of cellular damage, others have little to do with injury [92-94]. Moreover, as further understanding of the distinct nature of CNCP in terms of their neurobiological and behavioural aspects are gained, the more it becomes clear that the management of CNCP is complexified by a variety of multifaceted needs, which are distinctively different from that of acute pain [422-426].

While the medical legitimacy of opioids per se is not disputed, the prolonged use of opioids in CNCP is greatly obscured by the lack of sufficient high quality evidence supporting their effectiveness and safety. This creates a level of uncertainty and a dilemma in clinical practice. In line with this, results from clinical trials and recent epidemiological data suggest a need for greater caution when considering opioids long-term in the management of chronic non-cancer pain, particularly with the use of stronger opioids (chapter 2 page 38).

In the UK, evidence from aggregated data suggests that there have been significant increases in the prescribing of opioids in the past decade, and several studies have pointed that the

increased trend has predominately been associated with non-cancer pain [213, 214, 216, 217, 219]. However, as demonstrated in the literature review in chapter 2, there is limited information on the extent of the prescribing of opioids for long-term use, and there is lack of clarity regarding the population prescribed the potent analgesics and the prescribing details of opioids in practice (page 38).

In light of this, this thesis was conducted to reconcile gaps in knowledge and to gain a greater understanding of non-cancer pain patients prescribed stronger opioids in primary care. The studies in the thesis used both cross-sectional and longitudinal study designs, and utilised statistical techniques such as univariate and multivariate regression analysis to evaluate the impact of various factors on the long-term use of strong opioids and on the patterns of healthcare use by the recipients.

Chapter 3 (page 76) assessed changes in strong opioid prescription use (Morphine, Fentanyl, Oxycodone and Buprenorphine) by non-cancer pain patients in primary care over an 11-year period (2000-2010). In particular, the chapter aimed to assess the prevalence and incidence of non-cancer pain patients prescribed the medications long-term, thus circumventing the use of prescription counts as the lone surrogate measure of medication use over time. Results showed a steady increase in the incidence and prevalence of long-term strong opioid prescribing in non-cancer pain patients throughout the study period. In particular, trends of greater yearly growth in patients receiving an average supply of 91-120 days/year and >120 days/year were apparent. Although the majority of long-term users were prescribed long-acting formulations of strong opioids, it was evident that this was not always the case, pointing out further changes in the pattern of prescribing according to drug formulation of the four strong opioids over time.

Analysis of demographic data in chapter 4 (page 111) suggested that long-term users had a substantial number of pain and long-term comorbidities. It was estimated that the mean number of pain diagnoses was 3.0±2.2, and almost half of the users (47.10%) had three or more co-morbidities. Moreover, psychiatric or emotional comorbidities were prevalent in the users, and among long-term users 1 in 2 had been diagnosed with clinical depression and almost a quarter had anxiety diagnosed over the study period. Thus, this highlighted the commonness of multiple concurrent chronic conditions of a sample of community-dwelling non-cancer pain patients receiving long-term strong opioid treatment.

Chapter 5 (page 139) used the same data described in Chapter 4, but analysed the data as a panel dataset with repeated annual calculations of utilisation measures such as the number of prescriptions issued, day's supplied and oral morphine equivalent doses (OMED) for each user per year. Long-term users were found to have extended strong opioid exposure per year; the users' average yearly drug supply was 249.81±90.39 days, which almost covered an 8-month daily supply per year. Although the majority of long-term users had an annual mean daily dose of 95.88±109.03 mg/day, over a quarter of users were prescribed high annual mean daily doses that were greater than 120mg/day.

Multivariate analysis of the longitudinal data demonstrated a statistically significant link between the likelihood of users being long-term strong opioid users and a number of patient characteristics. Traits such as an advanced age beyond 50, female gender, being highly deprived, having a greater number of GP visitations and being prescribed psychoactive medications were significantly associated with chronic opioid therapy. Additionally, users who received an annual average dose of 101-120mg/day and those who exceeded 120-mg/day OMED, which is known to be a watchful dose (associated with increased risks of adverse

effects), had a 60%, and more than four-fold higher odds, of being long-term users, respectively.

Concurrently, the use of psychoactive medications including sedative-hypnotics was common, and more than a third of long-term users had benzodiazepine and non-benzodiazepine-based sedative-hypnotics prescribed during the study period. The average duration of supply of these medications was similar to the average length of supply of strong opioids per year (206.47±131.78 days and 208.04±128.57 days, respectively), which implied a chronic usage of the medications. The result also suggested a synergistic effect of the OMED dose in light of co-prescribing of benzodiazepine compared to users not prescribed the psychoactive drug. Long-term users who were co-prescribed benzodiazepines were found to have almost twice the average OMED dose of strong opioids compared with users not prescribed the psychoactive drug (113.51±129.19 mg/day versus 89.21±99.54 mg/day).

Finally, chapter 6 (page 183) found that long-term users were frequent users of primary healthcare. The median GP consultations-per-user-per-year was found to be 9 (IQR: 4, 15), which is higher than the national median rate of 5.31 per patient per year. This was likely to have been associated with the long-term management of strong opioid users in terms of their pain, comorbid conditions and mental health illnesses and concerns. Indeed, the study revealed that the use of primary care was influenced by a number of socio-demographic and clinical factors, which independently influenced the odds of a greater primary care consultation.

A striking finding of the chapter was an elevated all-cause in-patient hospital admission amongst long-term strong opioid users over the 11 years. This rose annually by 28.16%. The explanatory variables that were found to remain significantly linked to hospitalisation, both in the unadjusted and adjusted multivariate models, were GP visitations per year and the

prescribing of psychiatric medications, which suggested a consistent and an independent impact of these measures on the outcome.

The most common principle reason for long-term users' admission was identical to the main reason of re-admissions, which was for musculoskeletal-related pain disorders. Potential confounding by baseline demographics and time-varying clinical variables were adjusted for, and the analysis suggested that an oral morphine equivalent daily dose use equivalent to or greater than 100 mg/day increased the risk of musculoskeletal-related in-patient re-admissions amongst the long-term strong opioid users by 50%. Thus, if in-patient hospitalisation could supposedly be used as a proxy of patient-level health, then the increase in admissions, re-admissions and the main causes of the admissions would indicate a less optimal patient-health, to which pain management could be a contributor.

7.2 Commentary on methodology of the thesis: strengths and limitations

The findings of the thesis add to the body of knowledge of opioid use and outcomes in non-cancer pain patients in routine clinical practice, but the findings need to be interpreted with due consideration of the strengths and limitations of the methodology and analytical approach adopted in the studies.

A major strength of the work was that the dataset analysed stemmed from a high quality database. Previous pharmacoepidemiological studies conducted in the UK on strong opioid prescribing have, by and large, been based on data with small sample sizes or a non-probable study sample, which have yielded non-generalizable findings. The use of the Clinical Practice Research Datalink, which is one of the largest primary care databases in the UK and a source of patient medical records, provided the research with a real-world dataset from which a large

sample of non-cancer pain patients prescribed strong opioids could be identified, and this enabled patient-level details to be investigated under a set of observational study designs and realistic conclusions to be drawn.

Moreover, the use of hospital records from the Hospital Episode Statistics and its linkage with the primary care data was beneficial in that it enabled health outcomes such as serious hospital events to be traced for the study population during the observation time and evaluated. HES is known for its universal coverage, and the database covers all patients treated in an NHS hospital regardless of the source of funding, and hence includes private patients [384]. The accuracy of HES-coding system has been reviewed in a number of studies and the accuracy ratings of the database's administrative, diagnostic and medical interventional codes have been shown to be over 80% [427, 428]. This was likely to aid the accuracy of estimating the outcomes of interest in the current work.

However, a primary limitation in the current research was related to the extent of patient and practice-level information that was captured from the routinely collected data. The statistical prediction models of the outcomes of interest in chapter 5 and chapter 6 included a number of explanatory variables which are routinely recorded in CPRD, thus ensured that the results from the models were applicable to the UKs' general practice. However, several other important covariates, which may potentially have had an influence in predicting the odds of long-term strong opioid use and/or risk of hospitalisation, were not included. These include, at patient-level: severity of illness (pain intensity, severity of comorbidities), diagnostic testing (e.g. X-ray), further lifestyle measures (e.g. physical activity, diet), OTC-medication usage; and at general-practice-level: GP practice size, physicians' demographics, physicians' training status

and experience in the management of CNCP. This was mainly due to either the non-existing or extensively deficient recordings of the variables.

Long-term comorbid conditions covered in the Quality and Outcomes Framework (QOF) scheme defined by Read codes was judged to be suitable (as opposed to, for example, Charlson Comorbidity index or Barnett's list) in assessing the study patients' additional long-term morbidities apart from their pain disorder(s). The scheme incentivises and encourages UK GPs to maintain accurate records of patients' long-term diseases and health needs; thus, this increased the confidence that the recordings were likely to be complete and accurate [429]. The scheme was initially introduced in 2004 by the Department of Health, and it has since financially rewarded GPs throughout the UK for meeting outlined quality of care targets for a list of specific long-term conditions and organisational targets intended to improve performance [246]. However, the time-line covered by the present research and the start of follow-up in which clinical diagnosis of the study population were determined predated the initiation of QOF. This could have underestimated the quantification of QOF morbidities of patients who were registered with CPRD practices prior to 2004.

The application of multivariate regression analysis of the panel data in the studies enabled clarification of the relationship between multiple demographic and clinical variables that were measured at a single point in time at baseline and/or over multiple periods in time with the outcomes under investigation to be made. However, the studies, as with many pharmacoepidemiological studies that have examined independent and dependent variables simultaneously, was only possible to show with a level of certainty the significance of associations between explanatory variables and outcomes of interests, and as has been pointed out previously, not causality.

7.3 Implications of findings to policy and practice

Results generated in this thesis have several important implications for consideration. Findings from the prescribing trend suggests a shift in GPs' prescribing behaviour and indicates the need for continued attentiveness of non-cancer pain patients on prolonged use of strong opioids in clinical practice. Moreover, the picture that emerged was that the population examined represent complex clinical cases in that their pain diagnosis was not a stand-alone and was accompanied by other health-limiting conditions, which presents additional management health needs. This poses a number of potential clinical challenges in practice.

Firstly, primary care is undoubtedly a key substratum of the National Health Services and a setting for patients' initial and long-term management, and as it currently stands the GP contract in the UK sets consultation duration at 10-minutes irrespective of patients clinical profile, with the national average being 11-minutes and 42 seconds [430, 431]. However, research conducted in England, which have explored the content of GP consultations have highlighted that consultation times are compromised by the presence of patients' number of long-term conditions, with an added average of 2 minutes for each extra problem managed [307, 432]. Thus, it would be apparent that the study population of long-term strong opioid users would need longer consultation appointments to cover the scope of care of each of their presenting complaint, inclusive of patients' pain and its therapeutic management, which would place an undue strain on GPs' workload and resource use.

Moreover, in the current work, an increased frequency of GP visitations was not linked to a reduction in hospitalisation, suggesting that a greater emphasis would be needed on the content of the consultations. However, the evidence base for delivering services for patients with multiple (inclusive of pain either as the index condition or as a comorbid condition) chronic

long-term conditions in primary care is relatively sparse and predominantly based on clinical trials of interventions for single conditions [320, 433]. Indeed, a large systematic review by Smith SM et al. (2012) identified only 10 studies that evaluated clinical interventions for improving outcomes in patients with multimorbidities, and deduced that the evidence was limited and that many studies focused on the effects of multimorbidities on patients and the healthcare system as opposed to assessing interventions [433].

The management of patients with long-term conditions have traditionally been interchangeable between primary and secondary care with diagnosis and treatment often instigated in secondary care and patients' follow up conducted in primary care. However, over time and with the publication of a sequence of healthcare policies related to the management of long-term conditions, responsibility for chronic morbidities has increasingly shifted to primary care [434-436]. To date, and with the inception of several National Service Frameworks (QOF being a key National Service Framework), standards of care have been outlined for a specific number of long-term conditions [246]. However, as briefly discussed in chapter 4 (page 137), the management frameworks remain to be single-disease oriented, which may undermine the holistic care of patients with multiple co-occurring chronic conditions equivalent to the patient population examined in this thesis.

What this means for the current study population is that they would more likely require an integrated care response to their long-term health that is targeted towards pain management, but which also considers all (multiple) of their other health needs. The concept, which is broadly defined and described in the literature, refers to an integration of interdisciplinary care across specialisations that is ideally incorporated into patients' routine primary care, with a shared decision-making that results in a single combined long-term treatment plan adapted to

address patients' (complex) multitude of health problems [437, 438]. The care draws on different working dimensions such as the type of integration, the extent of services involved and the level of integration needed.

Leutz W (1999) argued that service users' needs should be at the center of integrated care, reasoning that patients with higher levels of needs, reflected by a degree of instability, chronicity of conditions, duality and complexity of treatments, as well as the general impact of conditions on patients' life, would require a more comprehensive integrated health management, with or without a social approach, than patients with lower levels of health needs [438]. Currently, at the service delivery level, the model that closely encapsulates the theoretical aspects of integrated care is 'case management' in primary care. This involves the identification of at-risk patients (typically defined in terms of at risk of secondary admissions), assessment of their health needs and organizing and coordinating care between different health care professionals. However, although its delivery has been encouraged in the recent modifications to the NHS GP contract (in the unplanned admissions enhanced service section) its provision has been highlighted to vary considerably across the country, and details of its practical application remains unclear [439, 440]. Moreover, the utilisation of case management for ('at-risk') chronic non-cancer pain patients with general long-term multimorbidities is less known.

Ultimately, patients with multimorbidities, polypharmacy and those who are recipients of long-term and high doses of strong opioids represent an obvious priority group for targeted reviews and a consideration for integrated care. The thesis has demonstrated the feasibility of identifying these patients through clinical information routinely collected from GP data. One way of facilitating this in practice would be to incorporate computerized triggered alerts that prompt physicians when a combinations of patient-specific characteristics that have been

shown to increase the likelihood of the use of strong opioids long-term, increase (high) dose use, and increase the risk of hospitalization are found in order to support appropriate early interjection of risk-management and preventative measures tailored to the patients' needs. The computerized alert system would further be beneficial in evaluating clinical decision-making if it also incorporates space for documenting reasons for annulling any national recommendations.

Findings of the high strong opioid dose use in the present research underscores the importance of routine close patient reviews to ensure patient safety. This also highlights the need for increased awareness, through educational training and informational campaigns to patients and practitioners alike, about the risks associated with strong opioids, particularly at higher doses. There also needs to be an emphasis placed on the insufficiency of evidence supporting the effectiveness of opioid use at high doses, which should further discourage unsafe-dose prescribing.

Moreover, attention is to be drawn to the possibility of a continuum of a vicious dose-escalation cycle that could overtly occur with long-term opioid therapy, and which could be attributed to the complex pharmacological nature of the high-risk drugs. For example, opioid tolerance combined with an unsatisfactory degree of analgesia could result in the consideration of dose increases to achieve pain relief; however, if tolerability becomes satisfactory, dose-escalation starts to compromise safety and efficacy. Concurrently, if intolerability is re-gained, this could oversee a re-consideration of dose increase in an effort to re-balance tolerability and analgesia; and thus, a vicious cycle of dose-tolerance balance may continue [(208)]. Therefore, though awareness through educational resources is crucial, the use of educational awareness

alone may not be adequate, and it may be useful to combine this with incentives to use best practice when considering opioid dosing in primary care.

The prolonged concomitant use of psychoactive medications, particularly sedative-hypnotics, highlights the existence of conditions such as long-lasting anxiety with chronic pain; indeed, a quarter of the study population had a diagnosis of anxiety. Unwittingly, the use of benzodiazepines may seem ideal in patients whose anxiety and mood disorders or insomnia is common and long-lasting. However, similar to opioids, robust evidence of effectiveness only exists for benzodiazepines' short-term use and evidence supporting their long-term use is lacking [(441)]. However, unlike antipsychotics where their adverse interaction with opioids is limited due to differences in metabolic pathways, benzodiazepines share many similar pharmacological traits with opioids, and their combination can result in significant safety risk. Current official recommendations on the use of benzodiazepines state that the agents could be instigated for short-term uses of 4-6 weeks, and there is less support for their treatment over longer periods than recommended [(442)].

In addition, the deleterious and serious interaction that has been affirmed from empirical studies between opioids and psychoactive medications makes their long-term combination a wary practice. It was beyond the scope of the study to examine the consequences of the concomitant use of the drug classes. However, careful patient selection prior to opioids treatment-initiation and in the consideration of chronic opioid use could help in lessening the likelihood of unwarranted drug-drug complications.

Moreover, at patient-level; educational intervention with the possibility of incorporating informed consent about the risks and benefits of prolonged concomitant use of benzodiazepines

would be a beneficial first step. Alongside this, promotion of non-pharmacological treatment modalities, such as CBT aimed at anxiety-prone non-cancer pain patients, may aid in the long-term management of the disorder and reduce prolonged need for sedative-hypnotics.

Cognitive behavioural therapy could also prove to be useful in supporting patients with self-management of chronic non-cancer pain. Several studies, including randomized controlled trials, have found beneficial outcomes of self-efficacy with CBT in the management of various pain conditions [82, 83, 443]. However, there is currently a significant gap in the application of the approach in clinical practice, which may be a possible avenue for prospective research consideration [91].

Meanwhile, hospital admissions and readmissions are regarded as a major source of monetary capacity and a resource pressure on the National Health Service, with re-admissions occurring within a month of discharge incurring an estimated annual cost of £2.6 billion [444]. To reduce such costs, the Department of Health introduced (in 2011) a non-payment policy for 30-day re-admissions; the impact of the policy on NHS care is yet to be evaluated. However, the policy provides guidance to local commissioners on restricting re-imbursements for the care and treatment of 30-day re-admissions of all causes but exclusive of re-admissions related to cancer, obstetric, paediatric, mental health and re-admission related to previous self-discharging [445].

The policy is based on the rationale that re-admissions within a month are unnecessary and signify suboptimal or premature care of initial admissions, and that savings made through the policy's application would be re-invested to support patients' care following discharge. It has been emphasised that for any intervention that is intended to improve admission rates to be

effective, further studies would be unequivocally needed to continuously build upon existing information on the causes of admissions and re-admission, and provide a detailed account of patient-groups at risk [446].

Thus the patterns, causes and factors influencing the hospitalisation of the study population examined in this thesis contribute valuable knowledge to be considered in any risk mitigation and preventative strategies in this population-group. This should include additional assessment of patients' pain, particularly in those with: low back pain; unspecified back/spine (dorsal) pain and joint pain. This should be complemented by psychosocial assessments, referrals to pain management and other professional services for patients not responding to treatment, and for the assessment to be considered at an early stage of signs of therapeutic unresponsiveness and/or disease deterioration to harmonize continuum of care.

In addition, the timing of readmissions found in the current work indicates that timely pre-discharge planning and post-discharge follow-ups may maximize prevention efforts of the event, and because the majority of the re-admissions were comparable to the index admission, efforts to reduce re-admissions in this patient group should be specifically focused on the clinical care related to the index admission i.e. musculoskeletal pain, whilst still ensuring clinical attention to patients' general health. Close patient monitoring would also be needed for patients with traits linked to the susceptibility of hospitalisations with the possibility of incorporating pharmacist-led interventions (e.g. medicine reviews).

Lastly, an online resource ("Opioid Aware"), funded by Public Health to support prescribers to adhere to good prescribing practice of opioids, has recently been launched [47]. This would be an ideal platform to disseminate information on patient-related variables that can exert

influence on chronic strong opioid prescribing that may significantly impact risks of deleterious outcomes; awareness of this prior to strong opioid treatment therapy could both invoke and inform long-term planning of patient care.

7.4 Implications for future research

Future research would be needed to expand on the current findings. Given that clinical trials assessing opioid therapy in chronic non-cancer pain systematically excludes patients of similar traits to the population in the current work, a natural first step in this direction, that would be of critical clinical significance in satisfying key questions in this area of research, would involve prospectively assessing the extent to which the chronic prescribing patterns identified pose complications, such as adverse effects. Concurrently, the level or extent (particularly in relation to differential dose-levels) of strong opioid use that produces constructive benefits that could be objectively measured in primary care in terms of alteration in the level of pain intensity, function and quality of life in diverse population-groups would also be a complementary issue for enquiry.

Inadvertently, there is an increasing acknowledgement that reduction of long-term, high-dose usage is a clinical challenge. Whilst interventions of effective opioid cessations have been well studied and evidence-based in the context of opioid addiction, insufficient systematic research exists to inform clinical practice on effective methods to reduce or reverse chronic and/or high-dose opioid therapy in non-cancer pain patients and, as such, further research would be needed to delineate evidence for a safe and effective method, with a mindfulness of the tools available for general practitioners in general practice to aid such a process.

Although the thesis provided quantitative estimations of opioid-prescribing, further nascent research using qualitative methodology to investigate and understand perspectives, rationale and the decision-making process of GPs' selection procedure of patients for strong opioid therapy would be useful. Furthermore, qualitative research on the decision-making process of the continuity of long-term strong opioid treatment and selection process of patient referred/not referred to specialist pain management would be useful to shed further light on and gain a deeper understanding of the current findings. This would also, in turn, facilitate the understanding of potential gaps and challenges of care for CNCP from physicians' perspective.

Furthermore, little research is currently in existence on the lived experiences of patients with CNCP treated with strong opioids long-term, and further work in the form of descriptive or interpretive qualitative methods would be timely to elucidate patients' medication experience relative to patterns of use. This would aid in identifying unmet needs of this population group, and facilitating strategies to meet patients' needs.

Following on from the estimated extent of primary and secondary healthcare use in this work, economic evaluation of the healthcare resource used (inclusive of the cost of strong opioid prescribing) would be of value for further research to help stakeholders responsible for healthcare budgeting to cost-effectively respond and plan the care of the population group.

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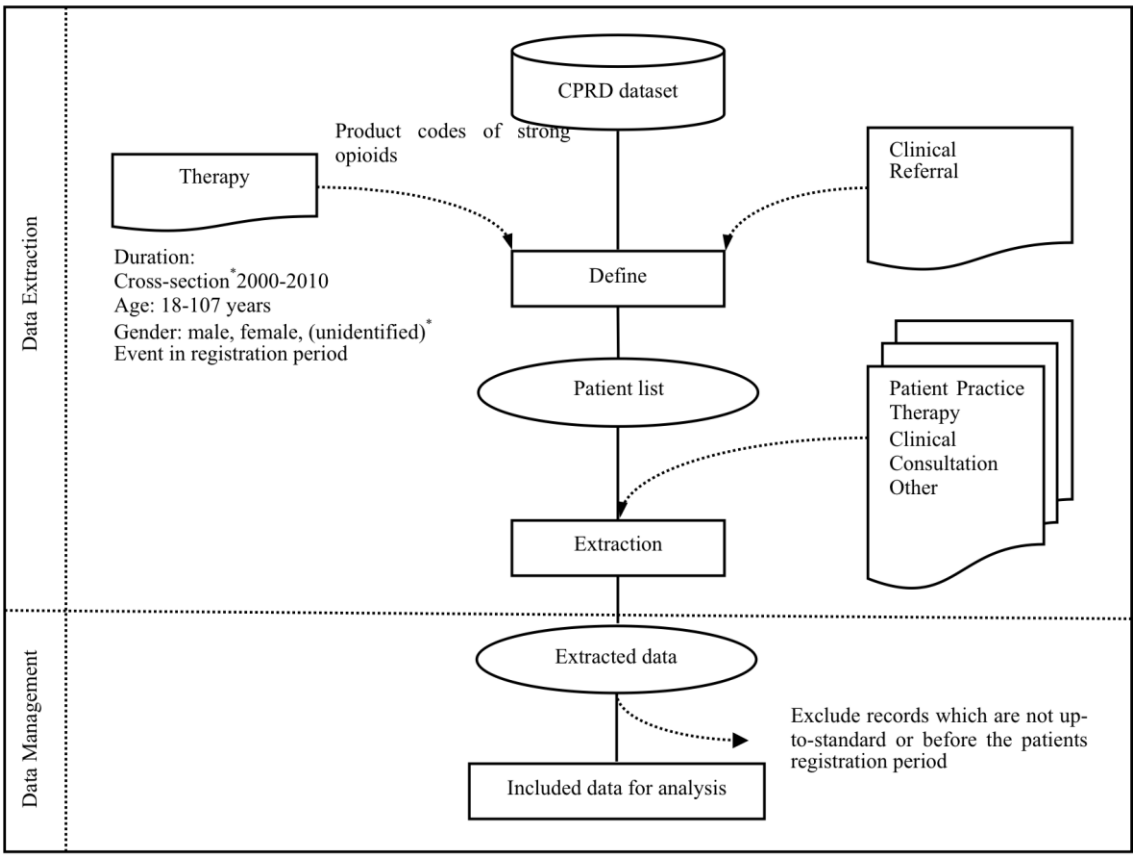
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Appendices

Appendix 1 Data extraction procedure in the Clinical Practice Research Datalink



Appendix 2 Literature search strategy

OVID MEDLINE

1. Opioid*.mp.
2. exp Analgesics, opioid/
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine)
4. narcotic$.mp.
5. exp Narcotics/
6. or/1-5
7. (chronic$ adj3 pain$)
8. exp Chronic Pain/
9. 7 or 8
10. 6 and 9
11. Limit 10 to (English language and human and yr= “1996-2016”)

PsychInfo

1. Opioid*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or codeine, deltorphin, dextromethorphan, dezocine, dihydrocodeine, dihydromorphine, enkephalin, ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or hydrocodone or

hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine).mp.

3. 1 or 2

4. (Chronic and pain).mp.

5. 3 and 4

6. (Random$ or control$ or trial or cohort or prospective or retrospective).mp.

7. 6 and 7

8. Limit 7 to (english language and human and yr=”1996-2016”)

CINAHL

1. (MH “Analgesics, opioid”) OR (MH “Narcotics”) OR (MH ”alfentanil”) OR “alfentanil” OR (MH “Alphaprodine”) OR “alphaprodine” OR “beta-casomorphins” OR (MH “Buprenorphine”) OR “buprenorphine” (MH “Codeine”) OR “codeine” OR “deltorphin” OR (MH “Dextromethorphan”) OR “dextromethorphan” OR “dezocine” OR “dihydrocodeine” OR “dihydromorphine” OR (MH “Enkephalins”) OR “enkephalin” OR “ethylketocyclazocine” OR “ethylmorphine” OR “etorphine” OR (MH “Fentanyl”) OR “fentanyl” OR “hydrocodone” OR (MH “Dihydromorphinone”) OR “hydromorphone” OR “ketobemidone” OR levorphanol” OR “lofentanil” OR (MH “Meperidine”) OR “meperidine” OR “meptazinol” OR “methadyl acetate” OR “(MH “Methadone”) OR “methadone” OR (MH “Nalbuphine”) OR (MH “Opium”) OR (MH “Morphine”) OR “morphine” OR (MH “Oxycodone”) OR “oxycodone” OR “oxymorphone” OR (MH ”Pentazocine”) OR “pentazocine” OR (MH “Propoxyphene”) OR “propoxyphene” OR “remifentanil” OR (MH “Sufentanil”) OR “sufentanil” OR “tilidine.”

2. (MH “Chronic Pain”) OR “chronic pain”

3. 1 and 2

4. “random*” OR “control*” OR “trial” OR “cohort” OR “prospective” OR “retrospective”

5. 3 and 4 (Limit published date: 1996-2016, english language)

Cochrane Library: Cochrane Central Register for Controlled Trials & Cochrane Database of Systematic Reviews

1. Analgesic, opioid$.mp.

2. narcotic$.mp.

3. (alfentanil or alphaprodine or beta-casomorphines or buprenorphine or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or hydrocodone or hydromorphone or kentobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine).mp.

4. or/1-4

5. Chronic pain

6. Chronic adj3 pain

7. 5 or 6

8. Cancer

9. 4 and 7 not 8

Appendix 3 Study quality assessment tools

Cochrane Back Review Group criteria list for methodological quality assessment

Criteria		Answer
1	Was the method of randomization adequate?	Y/N/D
2	Was the treatment allocation concealed?	Y/N/D
3	Were the groups similar at baseline?	Y/N/D
4	Were most important prognostic indicators similar between groups?	Y/N/D
5	Was the patient blinded to the intervention?	Y/N/D
6	Was the care provider blinded to the intervention?	Y/N/D
7	Was the outcome assessor blinded to the intervention?	Y/N/D
8	Were the co-interventions avoided or similar?	Y/N/D
9	Was the compliance acceptable in all groups?	Y/N/D
10	Was the dropout rate described and acceptable?	Y/N/D
11	Was the timing of the outcome assessment in all groups similar?	Y/N/D
Overall quality scoring: 1=Yes, 0=No or Don't know: <6= low, ≥6= high		

Adapted from Berger VW et al (2009) [447]. Y: yes, N: no, D: don't'know

Oxman and Guyatts'criteria for quality assessment of systematic reviews

Criteria		Answer
1	Were the search methods reported?	Y/N/U
2	Was the search comprehensive?	Y/N/U
3	Were the inclusion criteria reported?	Y/N/U
4	Was selection bias avoided?	Y/N/U
5	Were the validity criteria reported?	Y/N/U
6	Was validity assessed appropriately?	Y/N/U
7	Were the methods used to combine studies reported?	Y/N/U
8	Were the findings combined appropriately?	Y/N/U
9	Were the conclusions supported by the reported data?	Y/N/U
10	What was the overall scientific quality of the overview?	Y/N/U
Overall quality scoring: 1=Yes, 0=No or Unclear		

Extensive flaws		**Major Flaws**		**Minor Flaws**		**Minimal Flaws**
1	2	3	4	5	6	≥7

Adapted from Oxman AD, Guyatt GH (1991) [139]. Y: yes, N: No, U: unclear

(Continued) Appendix 3 Study quality assessment tools

The Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I)

Criteria		**Answer**
1. Confounding	1.1 Is there potential for confounding of the effect of intervention in this study? 1.2. Was the analysis based on splitting participants' follow up time according to intervention received? 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? 1.5 Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? 1.8. Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	NA/Y/PY/PN/N/NI
2. Study Selection	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? 2.2. Were the post-intervention variables that influenced selection likely to be associated with intervention? 2.3 Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? 2.4. Do start of follow-up and start of intervention coincide for most participants? 2.5.Were adjustment techniques used that are likely to correct for the presence of selection biases?	NA/Y/PY/PN/N/NI

Adapted from Sterne JA et al. (2016) [(140)] (version for cohort-type studies), NA: not applicable, Y: yes, PY: partially yes, PN: partially no, N: no, NI: no information

(Continued) Appendix 3 Study quality assessment tools

The Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I)

Criteria		**Answer**
3. Classification of Intervention	3.1 Were intervention groups clearly defined? 3.2 Was the information used to define intervention groups recorded at the start of the intervention? 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	NA/Y/PY/PN/N/NI
4. Deviation from intervention	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? 4.2. Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? 4.3. Were important co-interventions balanced across intervention groups? 4.4. Was the intervention implemented successfully for most participants? 4.5. Did study participants adhere to the assigned intervention regimen? 4.6. Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	NA/Y/PY/PN/N/NI
5. Missing data	5.1 Were outcome data available for all, or nearly all, participants? 5.2 Were participants excluded due to missing data on intervention status? 5.3 Were participants excluded due to missing data on other variables needed for the analysis? 5.4 Are the proportion of participants and reasons for missing data similar across interventions? 5.5 Is there evidence that results were robust to the presence of missing data?	NA/Y/PY/PN/N/NI
6. Measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received? 6.2 Were outcome assessors aware of the intervention received by study participants? 6.3 Were the methods of outcome assessment comparable across intervention groups? 6.4 Were any systematic errors in measurement of the outcome related to intervention received?	NA/Y/PY/PN/N/NI

NA: not applicable, Y: yes, PY: partially yes, PN: partially no, N: no, NI: no information

(Continued) Appendix 3 Study quality assessment tools

The Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I)

Criteria		Answer
7. Reported results	Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome *measurements* within the outcome domain? 7.2 ... multiple *analyses* of the intervention-outcome relationship? 7.3 ... different *subgroups*?	NA/Y/PY/PN/N/NI

Adapted from Sterne JA et al. (2016) [(140)] (version for cohort-type studies), NA: not applicable, Y: yes, PY: partially yes, PN: partially no, N: no, NI: no information

Appendix 4 Characteristics of RCTs and open-label trials of safety and efficacy of opioids in CNCP (not in reviewed systematic reviews)

Author, year	Participants, length of therapy, study method	Intervention	Main Findings	Quality (score)
Taber L et al., 2016 [448]	N=410 76-weeks Open-label trial	Hydrocodone-oral	Discontinuation was at 22%. Pain intensity was reduced from baseline (mean pain score 6.1 to 3.8), but treatment adverse effects were reported.	Low (5/11)
Arora S et al., 2014 [147]	N=395 Up to 12 months Open-label trial	Oxycodone-oral and Naltrexone-hydrochloride (ALO-02)	Small reduction in pain severity was noted with Oxycodone (mean change from baseline; -1.3 ±2.32) and the addition of Naltrexone did not alter clinical effects. Discontinuation due to adverse effects (31.65%) and lack of pain relief (15.61%) were common.	Low (3/11)
Hale ME et al., 2007 [146]	N=329 12 weeks RCT	Oxymorphone-ER-oral	Oxymorphone ER reduced average pain intensity compared to placebo over 12-weeks. However, 53% experienced adverse effects and 30% discontinued treatment.	High (10/11)
Trenkwalder C et al., 2013 [449]	N=306 12-weeks RCT	Oxycodone ER-oral	Oxycodone ERs' efficacy was demonstrated up to 12 weeks (mean change in pain intensity from baseline was greater than placebo; -16.5±11.3 versus -9.4±10.9), however adverse effects were frequent with Oxycodone ER (57%).	High (10/11)
Ueberall MA et al., 2016 [148]	N=901 12 weeks Open-label trial	Oxycodone, Oxycodone/Naloxone and Morphine-oral	Results suggest improvements in quality of life (mean change in weighted EQ-5D score by 0.33±0.32 points) over 12-weeks in chronic low back pain. However, discontinuation rate with active the drugs was high (35.5%) and mainly due to adverse effects.	Low (5/11)
Richarz U et al., 2013 [450]	N=112 52-weeks Open-label trial	Hydromorphone ER and Oxycodone CR-oral	Small decrease in pain severity was detected with Hydromorphone ER and Oxycodone CR at end of 52-weeks (mean change in pain intensity from baseline; -2.9±0.3 and -2.8±0.3 respectively). Majority of patients reported adverse effects; 84% with Hydromorphone ER, 91% with Oxycodone CR	Low (5/11)
Yarlas A et al., 2016 [451]	N=541 (trial 1), N=441 (trial 2) 12-weeks RCT	Buprenorphine transdermal	Buprenorphine transdermal generated a small improvement in sleep quality in patients with chronic low back pain compared to placebo over 12-weeks; mean difference in sleep problems index score d=0.32.	High (9/11)

* RCT: randomized controlled trial, CR: controlled release, ER: extended release, SR: sustained release

(Continued) Appendix 4 Characteristics of RCTs and open-label trials of safety and efficacy of opioids in CNCP

Author, year	Participants, length of therapy, study method	Intervention	Main Findings	Quality (score)
Ueberall MA et al., 2015 [452]	N=453 12-weeks Open-label trial	Oxycodone, Oxycodone/Naloxone and Morphine-oral	Greater reduction in pain intensity, function and tolerability was found with Oxycodone//Naloxone than either Oxycodone or Morphine in chronic low back pain.	Low (5/11)
Rauck RL et al., 2016 [144]	N=444 12-weeks Open-label trial	Buccal Buprenorphine	There was a >30% reduction in pain intensity with buccal Buprenorphine (63%) compared to placebo (47%) in chronic low-back pain. However, 23.5% discontinued treatment and 72.1% experienced ≥ 1 adverse effect(s).	High (8/11)
Kosinski M et al., 2007 [453]	N=815 12 weeks RCT	Oral Tramadol ER	Mean pain reduction with Tramadol was -30.4mm and -21.5mm for placebo at 12-weeks in patients with chronic osteoarthritis. Pain related sleep disturbance was reduced in Tramadol subjects than placebo (51% vs 42%, p=0.022). However 15.3% discontinued therapy due to lack of efficacy and 19.9%-29.7% due to adverse effects.	High (9/11)
Miller K et al., 2014 [145]	N=541 12-weeks RCT	Transdermal Buprenorphine	Improvement in the ability to preform various daily activities was reported for Buprenorphine transdermal compared to placebo in chronic low-back pain over 12 weeks. Information on treatment discontinuation was not available.	High (8/11)
Florete OG et al., 2008 [454]	N=1,020 12-weeks RCT	Oral Tramadol ER	Compared with placebo Tramadol ER improved overall sleep score up to 12-weeks from baseline in patients with osteoarthritis. However, 45.4% discontinued treatment due to insufficient therapeutic effects and adverse effects.	High (9/11)
Fishman RL et al., 2007 [455]	N=552 12-weeks RCT	Oral Tramadol	Improvement in pain score of ≥30% was reported in 65% of Tramadol subjects compared with 50% of placebo subjects at 12 weeks in osteoarthritis. However 87% of Tramadol subjects reported adverse effects.	High (10/11)
Yarlas A et al., 2013 [456]	N=541 12-weeks RCT	Transdermal Buprenorphine	Improvement in various (12-SF-32v2) health-related quality of life items from baseline with Buprenorphine transdermal compared to placebo was reported up to 12 weeks in chronic low back pain. Information on discontinuation was not available.	High (8/11)

* RCT: randomized controlled trial, CR: controlled release, ER: extended release, SR: sustained release

(Continued) Appendix 4 Characteristics of RCTs and open-label trials of safety and efficacy of opioids in CNCP

Author, year	Participants, length of therapy, study method	Intervention	Main Findings	Quality (score)
Mitra F et al., 2013 [149]	N=46 12-months Open-label trial	Transdermal Buprenorphine and Fentanyl	Adverse effects and lack of pain relief were frequent and resulted in 41% of Buprenorphine users and 37.5% fentanyl users to discontinue treatment. A 3-point VAS reduction in pain was reported in 50% of Buprenorphine users and 43% of Fentanyl users. However, 31% of Buprenorphine and 57% Fentanyl subjects required additional pain relief medication.	Low (5/11)
Wallace M et al., 2010 [457]	N=113 6-months Open-label trial	OROS-Hydromorphone ER-oral	Discontinuation was at 25.9%. A small improvement in pain relief was reported from baseline till end of month 6 (mean change in pain score from baseline: -0.53±1.012). Treatment adverse effects were frequently reported (69.9%).	Low (4/11)

* RCT: randomized controlled trial, CR: controlled release, ER: extended release, SR: sustained release

Appendix 5 Characteristics of systematic reviews of safety and efficacy of opioids in CNCP

Author, year	Participants, length of therapy, study method	Intervention	Authors' conclusion	Quality (score)
Gaskell H et al., 2016 [458]	N=687 4-12weeks 5 RCTs	Oxycodone at any dose, by any route	Evidence supporting the efficacy of Oxycodone (as Oxycodone MR) in diabetic neuropathy or postherpetic neuralgia is of very low quality due to limitations in study methods, heterogeneity in pain conditions and insufficient data. Adverse effects were frequent.	Minimal Flaws (9/9)
Stannard C et al., 2016 [459]	N=94 12 weeks 1-RCT	Oral Hydromorphone ER	There was limited evidence to confirm the efficacy of Hydromorphine in neuropathic pain. Clinically meaningful efficacy over placebo was not reported and half of patients experienced adverse events.	Minimal Flaws (7/9)
Haroutiunian S et al., 2012 [460]	N=181 20 days-18 weeks 2-RCTs & 1 Case study	Oral Methadone	No conclusions can be made on the efficacy or harm of methadone in CNCP due to few data for pooled analysis.	Minor Flaws (6/9)
Chaparro LE et al., 2013 [130]	N=5,540 4 weeks- 3 months 15 RCTs	Opioids administered either alone or in combination with other interventions	There were no placebo-RCTs that confirmed the effectiveness and safety of opioid treatment long-term in chronic low back pain. Meanwhile there was evidence (low to moderate quality) of short-term opioid efficacy.	Minor Flaws (6/9)
McNicol E et al., 2013 [461]	N=1,237 >1 day- 12 weeks 31-RCTs	Opioids by any route except intrathecially and epidurally	Efficacy of opioids in neuropathic pain is ambiguous due to small size, short-term durations and dropout rates. Long-term RCTs are needed to draw unbiased conclusions on efficacy. Adverse effects were commonly reported.	Minimal Flaws (9/9)
Noble M et al., 2010 [151]	N=4893 6 months and over 1-RCT & 25-case series	Opioids by any route	Evidence supporting long-term opioid efficacy is weak and many patients discontinued treatment due to insufficient pain relief or adverse effects.	Minimal Flaws (9/9)
Derry S et al., 2015 [462]	N=258 12 weeks 1-RCT	Fentanyl by any route	There was insufficient evidence to support the efficacy and safety of fentanyl in chronic neuropathic pain. Almost all patients (90%) experienced adverse effects and 1 in 7 dropped out due to adverse events and 1 in 5 due to inadequate pain relief.	Minimal Flaws (7/9)

* RCT: randomized controlled trial, CR: controlled release, ER: extended release, SR: sustained release

(Continued) Appendix 5 Characteristics of systematic reviews of safety and efficacy of opioids in CNCP

Author, year	Participants, length of therapy, study method	Intervention	Authors' conclusion	Quality (score)
Cote J et al., 2014 [463]	N=1,190 12 weeks and over 1-RCT & 9-Observational studies	Sublingual Buprenorphine	Evidence is of insufficient quality to determine effectiveness of sublingual Buprenorphine for chronic pain. This is due to methodological weaknesses of included studies. No meta-analysis could be conducted	Minor Flaws (5/9)
Mayyas F et al., 2010 [464]	N=1,489 12 weeks 6-RCTs	Oral Oxymorphone CR	There was limited data due to small no of studies. The included studies suggested that Oxymorphone provided pain control for up to 12 weeks. Adverse effects were very common and a reason for high drop out rate (30-40%)	Minor Flaws (6/9)
Bekkering GE et al., 2011 [465]	N= >9,224 12-weeks and over 56-RCTs with open-label follow up	Morphine by any route	Morphine was not more effective or tolerable than other opioids and hence the use of Morphine as reference standard for chronic pain is not justified by the results. Evidence of included studies was of moderate quality.	Minimal Flaws (8/9)
Manchikanti L et al., 2011 [466]	N=10,142 12-weeks and over 21-open-label trials	Opioids administered either orally or topically	There was fair evidence to suggest pain relief with Tramadol in osteoarthritis over minimum of 12-weeks. However evidence of efficacy of other opioids for various CNCP was insufficient	Minimal Flaws (9/9)
Kalso E et al., 2004 [135]	N=1,145 ≤8 weeks and between 6-24 months 15-RCTs with open-label follow up	Opioids administered via any route	The small proportion of patients who continued treatment does not allow for a fair conclusion on long-term efficacy of opioids. However short-term efficacy was evident in neuropathic and musculoskeletal pain conditions. Adverse events were common and experienced by 80% of study participants.	Minimal Flaws (9/9)
Furlan AD et al., 2006 [134]	N=6,019 Up to 16 weeks 41-RCTs	Any opioids via any route	Weak and strong opioids were effective in reducing pain and improving function over average treatment duration of 5 weeks (1-16 weeks). However, treatment discontinuation was significant (33%).	Minimal Flaws (9/9)

* RCT: randomized controlled trial, CR: controlled release, ER: extended release, SR: sustained release

(Continued) Appendix 5 Characteristics of systematic reviews of safety and efficacy of opioids in CNCP

Author, year	Participants, length of therapy, study method	Intervention	Authors' conclusion	Quality (score)
Martell BA et al., 2007 [150]	N=1,008-effiacy trials N=758-substance abuse studies Up to 16 weeks 15-RCTs on efficacy 4-Observational studies on substance abuse	Oral, topical or transdermal opioids	Efficacy of long-term opioids is unclear. Meta-analysis of opioids compared with placebo or non-opioids did not show reduced pain, and a non-significant reduction in pain was reported between different opioids. Prevalence of lifetime substance use disorders was common and ranged from 36% to 56%.	Minimal Flaws (9/9)
Papaleontiou M et al., 2010 [154]	N=7,790 1.5-156 weeks 31-RCTs 9-Observational studies	Oral or transdermal opioids	There were significant reductions in pain intensity and improvement in physical function and mental health in older adults with CNCP with no comorbidities over short-term opioid use. Long-term efficacy is yet to be confirmed. Adverse effects were common (25%).	Minimal Flaws (9/9)
Devulder J et al., 2005 [467]	N=2,877 Over 6 weeks (maximum 3 months) 6-RCTs 5-Observational studies	Any opioids via any route	A significant improvement in quality of life from baseline was reported. However further methodologically sound studies is needed to confirm findings.	Minor Flaws (5/9)
Chou R et al., 2003 [153]	N=2,617 4 weeks-18 months 16-RCTs 8-Observational studies	Oral long-acting opioids	There is insufficient evidence to suggest differences in efficacy and safety between different long-acting opioids. There is also insufficient evidence to demonstrate that long-acting opioids is more effective and safer than short-acting opioids.	Minimal Flaws (7/9)

* RCT: randomized controlled trial, CR: controlled release, ER: extended release, SR: sustained release

Appendix 6 ROBINS-I-Risk of bias assessment of reviewed observational studies

Author, year	Confounding	Selection	Measurement of intervention	Missing data	Measurement of outcomes	Reported results	Overall
Altier N et al., 2001 (157)	●	●	●	?	●	●	★
Ashworth J et al., 2013 (162)	●	●	●	?	●	●	★
Banta-Green CJ et al., 2009 (196)	●	●	●	?	●	●	★
Boscarino JA et al., 2010 (197)	●	●	●	?	●	●	★
Braden JB et al., 2012 (161)	●	●	●	●	●	●	★
Carman WJ et al., 2011 (191)	●	●	●	●	●	●	★
Reid MC et al., 2002 (468)	●	●	●	?	●	●	★
Chen L et al., 2013 (167)	●	●	●	?	●	●	★
Cowan DT et al., 2003 (201)	●	●	●	?	●	●	★
Deyo RA et al., 2013 (188)	●	●	●	●	●	●	★
Dilokthornsakul P et al., 2016 (205)	●	●	●	●	●	●	★
Dublin S et al., 2015 (469)	●	●	●	?	●	●	★
Dunn, KM et al., 2010 (185)	●	●	●	?	●	●	★
Edlund MJ et al., 2014 (195)	●	●	●	?	●	●	★
Kaplovitch E et al., 2015 (186)	●	●	●	●	●	●	★
Eriksen J et al., 2003 (470)	●	●	●	?	●	●	★
Ferrari R et al., 2015 (471)	●	●	●	?	●	●	★
Franklin GM et al., 2009 (358)	●	●	●	?	●	●	★

Low: "comparable to well-performed randomized trial"
Moderate: sound for a non-randomized study but not comparable to rigorous randomized trial"
Serious: presence of " important problems"
Critical: "too problematic to provide any useful evidence on the effects of intervention"
No information [?]: insufficient information provided to determine risk bias
Overall risk bias: equal to the most severe level bias found in any domain

(Continued) Appendix 6 ROBINS-I-Risk of bias assessment of reviewed observational studies

Author, year	Confounding	Selection	Measurement of intervention	Missing	Measurement of outcomes	Reported results	Overall
Galski T et al., 2000 (180)	🟠	🟠	🟠	?	🟢	🟠	✪
Gardner-Nix JS et al., 1996 (155)	🟠	🟠	🟢	?	🟢	🔴	✪
Gianni W et al., 2011 (169)	🟠	🟢	🟡	?	🟢	🟢	✪
Gomes T et al., 2011 (206)	🟢	🟡	🟢	🟢	🟢	🟡	✪
Grattan A et al., 2012 (204)	🟢	🟢	🟢	?	🟢	🟢	✪
Haythornthwaite J et al., 1998 (170)	🟠	🟠	🟢	?	🟠	🟢	✪
Hojsted J et al., 2010 (198)	🟢	🟢	🟢	🟢	🟢	🟢	✪
Huffman KL et al., 2015 (194)	🟠	🟢	🟢	🟠	🟢	🟢	✪
Ivanova JI et al., 2013 (179)	🟠	🟢	🟢	?	🟢	🟢	✪
James MW et al., 2007 (184)	🟢	🟡	🟢	?	🟢	🟡	✪
Jungquist CR et al., 2012 (183)	🟠	🟢	🟢	🟢	🟢	🟢	✪
Kidner CL et al., 2009 (164)	🟢	🟡	🟢	?	🟢	🟠	✪
Li L et al., 2013 (189)	🟢	🟡	🟢	?	🟢	🟡	✪
Li L et al., 2013 (472)	🟢	🟢	🟢	?	🟢	🟢	✪
Liang Y et al., 2015 (207)	🟢	🟢	🟢	🟠	🟢	🟢	✪

Low: "comparable to well-performed randomized trial"
Moderate: sound for a non-randomized study but not comparable to rigorous randomized trial"
Serious: presence of " important problems"
Critical: "too problematic…to provide any useful evidence on the effects of intervention"
No information [?]: insufficient information provided to determine risk bias
Overall risk bias: equal to the most severe level bias found in any domain

(Continued) Appendix 6 ROBINS-I-Risk of bias assessment of reviewed observational studies

Author, year	Confounding	Selection	Measurement of intervention	Missing	Measurement of outcomes	Reported results	Overall
Mogri M et al., 2009 [182]	●	●	●	?	●	●	✪
Peng P et al., 2008 [172]	●	●	●	?	●	●	✪
Price LC et al., 2014 [311]	●	●	●	?	●	●	✪
Rhodin A et al., 2010 [187]	●	●	●	?	●	●	✪
Saunders KW et al., 2010 [190]	●	●	●	?	●	●	✪
Schneider JP et al., 2010 [199]	●	●	●	●	●	●	✪
Taylor WF et al., 2000 [158]	●	●	●	?	●	●	✪
Tennant F et al., 2016 [473]	●	●	●	?	●	●	✪
Uberall MA et al., 2012 [168-171]	●	●	●	●	●	●	✪
Wasan AD et al., 2009 [200]	●	●	●	●	●	●	✪
Webster LR et al., 2008 [181]	●	●	●	?	●	●	✪

Low: "comparable to well-performed randomized trial"
Moderate: sound for a non-randomized study but not comparable to rigorous randomized trial"
Serious: presence of " important problems"
Critical: "too problematic…to provide any useful evidence on the effects of intervention"
No information [?]: insufficient information provided to determine risk bias
Overall risk bias: equal to the most severe level bias found in any domain

Appendix 7 Product codes of strong opioids

Product code	Strong opioid
	Buprenorphine
6879	buprenorphine four-day patch 35mcg/hour
6917	buprenorphine four-day patch 52.5mcg/hour
11584	buprenorphine four-day patch 70mcg/hour
396	buprenorphine hydrochloride sublingual tablets 200micrograms
3064	buprenorphine hydrochloride sublingual tablets 400micrograms
7236	buprenorphine seven-day patch 10micrograms/hour
7238	buprenorphine seven-day patch 20micrograms/hour
7334	buprenorphine seven-day patch 5micrograms/hour
10205	BUTRANS patch 10micrograms/hour [NAPPPHARM]
13300	BUTRANS patch 20micrograms/hour [NAPPPHARM]
7555	BUTRANS patch 5micrograms/hour [NAPPPHARM]
3522	TEMGESIC sublingual tablets 0.2mg [RB PHARMA]
8017	TEMGESIC sublingual tablets 400micrograms [RB PHARMA]
5936	TRANSTEC patch 35mcg/hour [NAPPPHARM]
6040	TRANSTEC patch 52.5mcg/hour [NAPPPHARM]
6181	TRANSTEC patch 70mcg/hour [NAPPPHARM]
Product code	**Fentanyl**
39518	ABSTRAL sublingual tablets 100micrograms [PROSTRAKAN]
39756	ABSTRAL sublingual tablets 200micrograms [PROSTRAKAN]
41286	ABSTRAL sublingual tablets 300micrograms [PROSTRAKAN]
39987	ABSTRAL sublingual tablets 400micrograms [PROSTRAKAN]
40508	ABSTRAL sublingual tablets 600micrograms [PROSTRAKAN]
39799	ABSTRAL sublingual tablets 800micrograms [PROSTRAKAN]
29577	ACTIQ lozenge with applicator 1200micrograms [FLYNN]
26021	ACTIQ lozenge with applicator 1600micrograms [FLYNN]
13076	ACTIQ lozenge with applicator 200micrograms [FLYNN]
18174	ACTIQ lozenge with applicator 400micrograms [FLYNN]
25199	ACTIQ lozenge with applicator 600micrograms [FLYNN]
26908	ACTIQ lozenge with applicator 800micrograms [FLYNN]
14900	DUROGESIC DTRANS patch 100micrograms/hour [JANSSEN]
11982	DUROGESIC DTRANS patch 12micrograms/hour [JANSSEN]
7082	DUROGESIC DTRANS patch 25micrograms/hour [JANSSEN]
7107	DUROGESIC DTRANS patch 50micrograms/hour [JANSSEN]
7397	DUROGESIC DTRANS patch 75micrograms/hour [JANSSEN]
10922	DUROGESIC patch 100micrograms/hour [JANSSEN]
748	DUROGESIC patch 25micrograms/hour [JANSSEN]
5048	DUROGESIC patch 50micrograms/hour [JANSSEN]
5657	DUROGESIC patch 75micrograms/hour [JANSSEN]

(Continued) Appendix 7 Product codes of strong opioids

Product code	Fentanyl
39746	EFFENTORA buccal tablets 100micrograms [CEPHALON]
39929	EFFENTORA buccal tablets 200micrograms [CEPHALON]
40128	EFFENTORA buccal tablets 400micrograms [CEPHALON]
40434	EFFENTORA buccal tablets 600micrograms [CEPHALON]
40957	EFFENTORA buccal tablets 800micrograms [CEPHALON]
37719	FENTALIS RESERVOIR patch 100micrograms/hour [SANDOZ]
37779	FENTALIS RESERVOIR patch 25micrograms/hour [SANDOZ]
37923	FENTALIS RESERVOIR patch 50micrograms/hour [SANDOZ]
38365	FENTALIS RESERVOIR patch 75micrograms/hour [SANDOZ]
39723	fentanyl buccal tablets 100micrograms
40018	fentanyl buccal tablets 200micrograms
40576	fentanyl buccal tablets 400micrograms
42538	fentanyl buccal tablets 600micrograms
37968	fentanyl iontophoretic transdermal system 40micrograms/dose
15337	fentanyl lozenge with applicator 1200micrograms
24986	fentanyl lozenge with applicator 1600micrograms
11843	fentanyl lozenge with applicator 200micrograms
5651	fentanyl lozenge with applicator 400micrograms
5696	fentanyl lozenge with applicator 600micrograms
5697	fentanyl lozenge with applicator 800micrograms
45894	fentanyl nasal spray 100micrograms/dose
45092	fentanyl nasal spray 200micrograms/dose
41135	fentanyl nasal spray 50micrograms/dose
4691	fentanyl patch 100micrograms/hour
7126	fentanyl patch 12micrograms/hour
620	fentanyl patch 25micrograms/hour
757	fentanyl patch 50micrograms/hour
6298	fentanyl patch 75micrograms/hour
39469	fentanyl sublingual tablets 100micrograms
39590	fentanyl sublingual tablets 200micrograms
40940	fentanyl sublingual tablets 300micrograms
40098	fentanyl sublingual tablets 400micrograms
41348	fentanyl sublingual tablets 600micrograms
42399	fentanyl sublingual tablets 800micrograms
43089	INSTANYL nasal spray 100micrograms/dose [NYCOMED]
43617	INSTANYL nasal spray 200micrograms/dose [NYCOMED]
45598	INSTANYL nasal spray 50micrograms/dose [NYCOMED]
36040	MATRIFEN patch 100micrograms/hour [NYCOMED]
37928	MATRIFEN patch 12micrograms/hour [NYCOMED]
35968	MATRIFEN patch 25micrograms/hour [NYCOMED]
36211	MATRIFEN patch 50micrograms/hour [NYCOMED]

(Continued) Appendix 7 Product codes of strong opioids

Product code	Fentanyl
38351	MATRIFEN patch 75micrograms/hour [NYCOMED]
38553	MEZOLAR MATRIX patch 100micrograms/hour [SANDOZ]
37954	MEZOLAR MATRIX patch 12micrograms/hour [SANDOZ]
38031	MEZOLAR MATRIX patch 25micrograms/hour [SANDOZ]
39180	MEZOLAR MATRIX patch 50micrograms/hour [SANDOZ]
38326	MEZOLAR MATRIX patch 75micrograms/hour [SANDOZ]
39084	OSMACH patch 100micrograms/hour [RATIOPHARM]
39251	OSMACH patch 25micrograms/hour [RATIOPHARM]
37960	OSMACH patch 50micrograms/hour [RATIOPHARM]
41161	OSMACH patch 75micrograms/hour [RATIOPHARM]
45460	OSMANIL patch 100micrograms/hour [WINTHROP]
44487	OSMANIL patch 12micrograms/hour [WINTHROP]
42591	OSMANIL patch 25micrograms/hour [WINTHROP]
43152	OSMANIL patch 50micrograms/hour [WINTHROP]
42590	OSMANIL patch 75micrograms/hour [WINTHROP]
45439	PECFENT nasal spray 100micrograms/dose [ARCHIMEDES]
46354	PECFENT nasal spray 400micrograms/dose [ARCHIMEDES]
28189	TILOFYL patch 100micrograms/hour [TILLOMED]
31053	TILOFYL patch 25micrograms/hour [TILLOMED]
22066	TILOFYL patch 50micrograms/hour [TILLOMED]
16618	TILOFYL patch 75micrograms/hour [TILLOMED]
42021	VICTANYL patch 100micrograms/hour [ACTAVIS]
45549	VICTANYL patch 25micrograms/hour [ACTAVIS]
44837	VICTANYL patch 50micrograms/hour [ACTAVIS]
42576	VICTANYL patch 75micrograms/hour [ACTAVIS]
Product code	**Oxycodone**
5585	oxycodone hydrochloride capsules 10mg
7275	oxycodone hydrochloride capsules 20mg
6790	oxycodone hydrochloride capsules 5mg
5843	oxycodone hydrochloride modified release tablet 10mg
46187	oxycodone hydrochloride modified release tablet 120mg
45790	oxycodone hydrochloride modified release tablet 15mg
6608	oxycodone hydrochloride modified release tablet 20mg
45827	oxycodone hydrochloride modified release tablet 30mg
6708	oxycodone hydrochloride modified release tablet 40mg
6769	oxycodone hydrochloride modified release tablet 5mg
45929	oxycodone hydrochloride modified release tablet 60mg
6948	oxycodone hydrochloride modified release tablet 80mg
6609	oxycodone hydrochloride oral liquid 5mg/5ml
11405	oxycodone hydrochloride oral liquid concentrate 10mg/ml

(Continued) Appendix 7 Product codes of strong opioids

Product code	Oxycodone
39475	oxycodone hydrochloride with naloxone hydrochloride modified release tablet 10mg/5mg
39498	oxycodone hydrochloride with naloxone hydrochloride modified release tablet 20mg/10mg
40785	oxycodone hydrochloride with naloxone hydrochloride modified release tablet 40mg/20mg
40616	oxycodone hydrochloride with naloxone hydrochloride modified release tablet 5mg/2.5mg
5599	OXYCONTIN modified release tablet 10mg [NAPPPHARM]
45830	OXYCONTIN modified release tablet 120mg [NAPPPHARM]
45788	OXYCONTIN modified release tablet 15mg [NAPPPHARM]
7389	OXYCONTIN modified release tablet 20mg [NAPPPHARM]
45745	OXYCONTIN modified release tablet 30mg [NAPPPHARM]
9927	OXYCONTIN modified release tablet 40mg [NAPPPHARM]
7167	OXYCONTIN modified release tablet 5mg [NAPPPHARM]
45766	OXYCONTIN modified release tablet 60mg [NAPPPHARM]
10021	OXYCONTIN modified release tablet 80mg [NAPPPHARM]
9973	OXYNORM capsules 10mg [NAPPPHARM]
7372	OXYNORM capsules 20mg [NAPPPHARM]
6557	OXYNORM capsules 5mg [NAPPPHARM]
9874	OXYNORM liquid 5mg/5ml [NAPPPHARM]
7406	OXYNORM oral liquid concentrate 10mg/ml [NAPPPHARM]
39477	TARGINACT modified release tablet 10mg/5mg [NAPPPHARM]
39478	TARGINACT modified release tablet 20mg/10mg [NAPPPHARM]
40961	TARGINACT modified release tablet 40mg/20mg [NAPPPHARM]
40645	TARGINACT modified release tablet 5mg /2.5mg [NAPPPHARM]
Product code	**Morphine**
495	MST CONTINUS tablets 10mg [NAPPPHARM]
607	MST CONTINUS granules for suspension 20mg/sachet [NAPPPHARM]
655	morphine sulphate oral solution (unit dose) 10mg/5ml
1503	ORAMORPH oral solution 10mg/5ml [BOEH I HSP]
2957	MST CONTINUS tablets 30mg [NAPPPHARM]
2997	ORAMORPH SR tablets 10mg [BOEH I HSP]
3919	SEVREDOL tablets 10mg [NAPPPHARM]
4266	morphine sulphate tablets 10mg
4280	MST CONTINUS tablets 5mg [NAPPPHARM]
4476	MST CONTINUS granules for suspension 60mg/sachet [NAPPPHARM]
4477	MST CONTINUS tablets 60mg [NAPPPHARM]
4693	ORAMORPH oral solution (unit dose) 10mg/5ml [BOEH I HSP]
5555	SEVREDOL oral solution 10mg/5ml [NAPP]
5563	morphine sulphate 12 hour modified release capsules 20mg
5652	morphine sulphate 12 hour modified release capsules 50mg

(Continued) Appendix 7 Product codes of strong opioids

Product code	Morphine
5681	morphine sulphate modified release tablet 10mg
5714	MST CONTINUS tablets 15mg [NAPPPHARM]
5840	morphine sulphate oral solution 10mg/5ml
5991	MST CONTINUS tablets 100mg [NAPPPHARM]
6002	morphine sulphate 12 hour modified release capsules 10mg
6232	SEVREDOL tablets 20mg [NAPPPHARM]
6269	morphine sulphate concentrated oral solution 20mg/ml
6366	SEVREDOL tablets 50mg [NAPPPHARM]
6736	morphine sulphate modified release granules for oral suspension 20mg/sachet
7197	morphine sulphate 12 hour modified release capsules 30mg
7875	morphine sulphate modified release tablet 30mg
8039	MST CONTINUS tablets 200mg [NAPPPHARM]
8822	morphine sulphate modified release tablet 60mg
8876	ORAMORPH concentrated oral solution 20mg/ml [BOEH I HSP]
9137	morphine sulphate tablets 20mg
9183	morphine sulphate modified release tablet 100mg
9337	MXL modified release capsules 30mg [NAPPPHARM]
9342	MXL modified release capsules 60mg [NAPPPHARM]
9371	MXL modified release capsules 120mg [NAPPPHARM]
9381	MXL modified release capsules 90mg [NAPPPHARM]
9484	morphine sulphate 24 hour modified release capsules 60mg
9557	morphine sulphate modified release tablet 15mg
9602	morphine sulphate modified release tablet 5mg
9672	morphine sulphate modified release granules for oral suspension 100mg/sachet
9960	morphine sulphate 12 hour modified release capsules 60mg
10239	MXL modified release capsules 150mg [NAPPPHARM]
11342	ORAMORPH oral solution (unit dose) 30mg/5ml [BOEH I HSP]
11698	morphine sulphate 24 hour modified release capsules 30mg
11755	MORCAP SR modified release capsules 20mg [MAYNE]
11838	morphine sulphate modified release tablet 200mg
12591	morphine sulphate modified release granules for oral suspension 60mg/sachet
12604	MST CONTINUS granules for suspension 100mg/sachet [NAPPPHARM]
12889	ORAMORPH oral solution (unit dose) 100mg/5ml [BOEH I HSP]
12900	MST CONTINUS granules for suspension 30mg/sachet [NAPPPHARM]
13114	ZOMORPH modified release capsules 10mg [ARCHIMEDES]
13117	ZOMORPH modified release capsules 30mg [ARCHIMEDES]
13711	MORCAP SR modified release capsules 20mg [DBL]
13995	morphine sulphate 24 hour modified release capsules 200mg
13997	morphine sulphate modified release capsules 100mg
14050	morphine sulphate 12 hour modified release capsules 100mg
14063	ZOMORPH modified release capsules 100mg [ARCHIMEDES]

(Continued) Appendix 7 Product codes of strong opioids

Product code	Morphine
14156	morphine sulphate oral solution (unit dose) 30mg/5ml
14226	morphine sulphate modified release granules for oral suspension 30mg/sachet
15781	morphine sulphate 24 hour modified release capsules 90mg
15815	morphine sulphate tablets 50mg
15950	ZOMORPH modified release capsules 200mg [ARCHIMEDES]
15964	ZOMORPH modified release capsules 60mg [ARCHIMEDES]
16273	ORAMORPH SR tablets 30mg [BOEH I HSP]
17893	ORAMORPH SR tablets 60mg [BOEH I HSP]
17936	MXL modified release capsules 200mg [NAPPPHARM]
17943	SEVREDOL concentrated oral solution 20mg/ml [NAPP]
18166	morphine sulphate 12 hour modified release capsules 200mg
18734	ORAMORPH SR tablets 100mg [BOEH I HSP]
18801	MORCAP SR modified release capsules 100mg [MAYNE]
18881	MORPHGESIC SR tablets 10mg [AMDIPHARM]
19092	MORCAP SR modified release capsules 50mg [DBL]
19291	morphine sulphate oral solution (unit dose) 100mg/5ml
19317	OMNOPON tablets 10mg [ROCHE]
19449	MORPHGESIC SR tablets 30mg [AMDIPHARM]
19471	MORPHGESIC SR tablets 60mg [AMDIPHARM]
19477	MORPHGESIC SR tablets 100mg [AMDIPHARM]
22024	RHOTARD MORPHINE SR tablets 10mg [SOVEREIGN]
22026	RHOTARD MORPHINE SR tablets 30mg [SOVEREIGN]
22690	morphine sulphate 24 hour modified release capsules 120mg
22756	FILNARINE SR tablets 30mg [TEVA]
23060	MST CONTINUS granules for suspension 200mg/sachet [NAPPPHARM]
24453	MORCAP SR modified release capsules 100mg [DBL]
26283	FILNARINE SR tablets 10mg [TEVA]
26284	FILNARINE SR tablets 100mg [TEVA]
27058	FILNARINE SR tablets 60mg [TEVA]
27749	morphine sulphate 24 hour modified release capsules 150mg
29020	morphine sulphate modified release granules for oral suspension 200mg/sachet
34477	MORPHINE SULPHATE oral solution 10mg/5ml [MARTINDALE]
40563	morphine sulphate modified release capsules 30mg
42380	morphine sulphate modified release capsules 10mg
43652	morphine sulphate modified release capsules 100mg
43657	morphine sulphate modified release capsules 200mg
45736	morphine sulphate modified release capsules 60mg

Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
318	B210.00	Malignant neoplasm of glottis
319	B21..00	Malignant neoplasm of larynx
779	B49..00	Malignant neoplasm of urinary bladder
780	B46..00	Malignant neoplasm of prostate
865	B32..00	Malignant melanoma of skin
1056	B5z..00	Malignant neoplasm of other and unspecified site NOS
1062	B10..00	Malignant neoplasm of oesophagus
1220	B13..00	Malignant neoplasm of colon
1599	B4A0.00	Malignant neoplasm of kidney parenchyma
1800	B141.00	Malignant neoplasm of rectum
1952	B580.00	Secondary malignant neoplasm of kidney
1986	B440.11	Cancer of ovary
2492	B33z.00	Malignant neoplasm of skin NOS
2587	B22z.11	Lung cancer
2744	B40..00	Malignant neoplasm of uterus, part unspecified
2744	B40..00	Malignant neoplasm of uterus, part unspecified
2747	B41..00	Malignant neoplasm of cervix uteri
2755	B....11	Cancers
2815	B133.00	Malignant neoplasm of sigmoid colon
2890	B430200	Malignant neoplasm of endometrium of corpus uteri
3213	B430.00	Malignant neoplasm of corpus uteri, excluding isthmus
3541	B48..00	Malignant neoplasm of penis and other male genital organs
3811	B134.00	Malignant neoplasm of caecum
3903	B22z.00	Malignant neoplasm of bronchus or lung NOS
3968	B34..00	Malignant neoplasm of female breast
4156	PE1..12	Sternomastoid tumour
4218	B541.00	Malignant neoplasm of parathyroid gland
4388	B020.00	Malignant neoplasm of parotid gland
4554	B454.00	Malignant neoplasm of vulva unspecified
4632	B33..00	Other malignant neoplasm of skin
4865	B10z.11	Oesophageal cancer
5116	B900011	Mixed parotid tumour
5198	B583000	Secondary malignant neoplasm of brain
5443	F122.00	Malignant neuroleptic syndrome
5637	B53..00	Malignant neoplasm of thyroid gland
5842	B58..00	Secondary malignant neoplasm of other specified sites
5932	BB06.00	[M]Tumour cells, uncertain whether benign or malignant
6751	BBC3.00	[M]Granulosa cell tumour NOS
6806	B12..00	Malignant neoplasm of small intestine and duodenum
6895	BB05.00	[M]Tumour cells, benign
6935	B131.00	Malignant neoplasm of transverse colon
7046	B43..00	Malignant neoplasm of body of uterus
7593	H51y700	Malignant pleural effusion
7654	B585.00	Secondary malignant neoplasm of bone and bone marrow
7805	B440.00	Malignant neoplasm of ovary
7982	B161200	Malignant neoplasm of common bile duct

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
8154	B576200	Malignant ascites
8166	B17..00	Malignant neoplasm of pancreas
8386	B11..00	Malignant neoplasm of stomach
8550	B542000	Malignant neoplasm of pituitary gland
8627	BB07.00	[M]Tumour cells, malignant
8771	B170.00	Malignant neoplasm of head of pancreas
8918	B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
9030	B55..00	Malignant neoplasm of other and ill-defined sites
9088	B130.00	Malignant neoplasm of hepatic flexure of colon
9237	B21z.00	Malignant neoplasm of larynx NOS
9303	1J09.00	Suspected bladder cancer
9470	B34z.00	Malignant neoplasm of female breast NOS
9505	B582600	Secondary malignant neoplasm of skin of breast
9618	B56..00	Secondary and unspecified malignant neoplasm of lymph nodes
9622	B525.00	Malignant neoplasm of cauda equina
10283	B01..00	Malignant neoplasm of tongue
10358	B222.00	Malignant neoplasm of upper lobe, bronchus or lung
10698	B450100	Malignant neoplasm of vaginal vault
10805	BB10.00	[M]Epithelial tumour, benign
10851	B51..11	Cerebral tumour - malignant
10864	B132.00	Malignant neoplasm of descending colon
10923	1J03.00	Suspected brain tumour
10946	B136.00	Malignant neoplasm of ascending colon
10949	B162.00	Malignant neoplasm of ampulla of Vater
10995	B5...00	Malignant neoplasm of other and unspecified sites
11035	B593.00	Primary malignant neoplasm of unknown site
11178	B702300	Warthin's tumour
11628	B1z0.11	Cancer of bowel
11754	BBCG.00	[M]Sclerosing stromal tumour
11991	B454.11	Primary vulval cancer
12323	B6...00	Malignant neoplasm of lymphatic and haemopoietic tissue
12335	B62y.00	Malignant lymphoma NOS
12389	B4A1.00	Malignant neoplasm of renal pelvis
12490	B550200	Malignant neoplasm of nose NOS
12499	Byu6.00	[X]Malignant neoplasm of breast
12582	B224100	Malignant neoplasm of lower lobe of lung
12870	B221.00	Malignant neoplasm of main bronchus
13243	B22..00	Malignant neoplasm of trachea, bronchus and lung
13252	B4...00	Malignant neoplasm of genitourinary organ
13558	1J00.00	Suspected lung cancer
14712	B00..00	Malignant neoplasm of lip
14792	B05..00	Malignant neoplasm of other and unspecified parts of mouth
14800	B11z.00	Malignant neoplasm of stomach NOS
15027	B62yz00	Malignant lymphoma NOS
15036	B626.00	Malignant mast cell tumours
15103	B577.00	Secondary malignant neoplasm of liver

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
15148	B47..00	Malignant neoplasm of testis
15169	B7J0.11	Glomus tumour
15182	B31z.00	Malignant neoplasm of connective and soft tissue, site NOS
15221	B220.00	Malignant neoplasm of trachea
15223	B4A2.00	Malignant neoplasm of ureter
15377	G200.00	Malignant essential hypertension
15504	B62y800	Malignant lymphoma NOS of lymph nodes of multiple sites
15543	BB01.00	[M]Neoplasm, uncertain whether benign or malignant
15644	B4A3.00	Malignant neoplasm of urethra
15684	B204.00	Malignant neoplasm of frontal sinus
15709	B1...00	Malignant neoplasm of digestive organs and peritoneum
15711	B510.00	Malignant neoplasm cerebrum (excluding lobes and ventricles)
15868	B335z00	Malignant neoplasm of skin of trunk, excluding scrotum, NOS
15907	B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
15976	B552.00	Malignant neoplasm of abdomen
15991	B506.00	Malignant neoplasm of choroid
16075	B30z.00	Malignant neoplasm of bone and articular cartilage NOS
16105	B160.00	Malignant neoplasm of gallbladder
16202	B333400	Malignant neoplasm of skin of nose (external)
16213	B572.00	Secondary malignant neoplasm of pleura
16241	B060.00	Malignant neoplasm of tonsil
16280	B550400	Malignant neoplasm of neck NOS
16297	B0z0.00	Malignant neoplasm of pharynx unspecified
16298	B18z.00	Malignant neoplasm of retroperitoneum and peritoneum NOS
16460	BBg2.00	[M]Malignant lymphoma, non Hodgkin's type
16500	B58z.00	Secondary malignant neoplasm of other specified site NOS
16704	B302.00	Malignant neoplasm of vertebral column
16760	B58y000	Secondary malignant neoplasm of breast
16915	B151.00	Malignant neoplasm of intrahepatic bile ducts
16967	B432.00	Malignant neoplasm of overlapping lesion of corpus uteri
17314	BBL7112	[M]Wilms' tumour
17366	BBF..00	[M]Soft tissue tumours and sarcomas NOS
17391	B221000	Malignant neoplasm of carina of bronchus
17404	1J08.00	Suspected prostate cancer
17475	B300A00	Malignant neoplasm of maxilla
17559	B1z0.00	Malignant neoplasm of intestinal tract, part unspecified
17841	B481.00	Malignant neoplasm of glans penis
17887	B62x.00	Malignant lymphoma otherwise specified
17912	B042.00	Malignant neoplasm, overlapping lesion of floor of mouth
18065	BBC7.00	[M]Sertoli-Leydig cell tumour
18245	B330.00	Malignant neoplasm of skin of lip
18266	BBf0.00	[M]Granular cell tumour NOS
18314	B30..00	Malignant neoplasm of bone and articular cartilage
18354	B33y.00	Malignant neoplasm of other specified skin sites
18613	B120.00	Malignant neoplasm of duodenum

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
18616	B58y.00	Secondary malignant neoplasm of other specified sites
18617	B51..00	Malignant neoplasm of brain
18618	B335300	Malignant neoplasm of skin of abdominal wall
18619	B137.00	Malignant neoplasm of splenic flexure of colon
18632	B135.00	Malignant neoplasm of appendix
18638	BB81.12	[M]Ovarian mucinous tumour
18678	B224000	Malignant neoplasm of lower lobe bronchus
18690	BBe..00	[M]Nerve sheath tumour
18712	B4A..11	Renal malignant neoplasm
18882	B006.00	Malignant neoplasm of overlapping lesion of lip
18894	1J07.00	Suspected endometrial cancer
19141	B44..00	Malignant neoplasm of ovary and other uterine adnexa
19144	Byu4.00	[X]Melanoma and other malignant neoplasms of skin
19162	B493.00	Malignant neoplasm of anterior wall of urinary bladder
19226	B513.00	Malignant neoplasm of parietal lobe
19318	B112.00	Malignant neoplasm of pyloric antrum of stomach
19321	B311300	Malignant neoplasm of connective and soft tissue of hand
19415	B0...00	Malignant neoplasm of lip, oral cavity and pharynx
19423	B35..00	Malignant neoplasm of male breast
19444	Byu4100	[X]Malignant melanoma of skin, unspecified
19475	B471.00	Malignant neoplasm of descended testis
19657	B911000	Malignant hydatidiform mole
19945	B582.00	Secondary malignant neoplasm of skin
20092	B04..00	Malignant neoplasm of floor of mouth
20160	B50..00	Malignant neoplasm of eye
20166	B45z.00	Malignant neoplasm of female genital organ NOS
20292	B02..00	Malignant neoplasm of major salivary glands
20350	BBQ4.14	[M]Yolk sac tumour
20685	B346.00	Malignant neoplasm of axillary tail of female breast
21173	BBL5.00	[M]Mullerian mixed tumour
21207	BB...11	[M]Tumour morphology
21319	BBC0.13	[M]Testicular stromal tumour
21330	B180.00	Malignant neoplasm of retroperitoneum
21435	BBC0.12	[M]Ovarian stromal tumour
21590	B58y500	Secondary malignant neoplasm of prostate
21620	B111.00	Malignant neoplasm of pylorus of stomach
21698	B221z00	Malignant neoplasm of main bronchus NOS
21882	BBP8.00	[M]Adenomatoid tumour NOS
21868	BB02.00	[M]Neoplasm, malignant
22146	B581100	Secondary malignant neoplasm of bladder
22156	BB08.00	[M]Malignant tumour, small cell type
22158	B630000	Malignant plasma cell neoplasm, extramedullary plasmacytoma
22290	B313.00	Malignant neoplasm of connective and soft tissue of thorax
22330	BBX..00	[M]Giant cell tumours
22441	B212.00	Malignant neoplasm of subglottis
22524	B58yz00	Secondary malignant neoplasm of other specified site NOS

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
22893	B06..00	Malignant neoplasm of oropharynx
22894	B110100	Malignant neoplasm of cardio-oesophageal junction of stomach
23380	B340000	Malignant neoplasm of nipple of female breast
23389	B200.00	Malignant neoplasm of nasal cavities
23399	B344.00	Malignant neoplasm of upper-outer quadrant of female breast
23433	B161.00	Malignant neoplasm of extrahepatic bile ducts
23480	B335900	Malignant neoplasm of perianal skin
23861	B551100	Malignant neoplasm of chest wall NOS
24048	B180200	Malignant neoplasm of retrocaecal tissue
24370	B142.00	Malignant neoplasm of anal canal
24397	B061.00	Malignant neoplasm of tonsillar fossa
24511	BB09.00	[M]Malignant tumour, giant cell type
24675	B07..00	Malignant neoplasm of nasopharynx
24805	F4G1111	Pseudotumour of orbit
24852	B016.00	Malignant neoplasm of lingual tonsil
25215	1J0D.00	Suspected upper gastrointestinal cancer
25245	B336400	Malignant neoplasm of skin of finger
25396	1J0E.00	Suspected lower gastrointestinal cancer
25535	B150.00	Primary malignant neoplasm of liver
25602	B326400	Malignant melanoma of finger
25810	BBM0.00	[M]Brenner tumours
25886	B222100	Malignant neoplasm of upper lobe of lung
26034	B591.00	Other malignant neoplasm NOS
26134	B064000	Malignant neoplasm of epiglottis, free border
26165	B211.00	Malignant neoplasm of supraglottis
26393	B152.00	Malignant neoplasm of liver unspecified
26448	B060000	Malignant neoplasm of faucial tonsil
26454	B45X.00	Malignant neoplasm/overlapping lesion/feml genital organs
26478	SN5y000	Malignant hyperpyrexia due to anaesthetic
26813	B21y.00	Malignant neoplasm of larynx, other specified site
26814	BB5D512	[M]Hepatoma, malignant
26853	B340.00	Malignant neoplasm of nipple and areola of female breast
26872	1J06.00	Suspected cervical cancer
26878	1J0C.00	Suspected testicular cancer
27363	16	[M]Meningioma, malignant
27370	B333.00	Malignant neoplasm skin of other and unspecified parts face
27391	B576100	Secondary malignant neoplasm of peritoneum
27449	B554.00	Malignant neoplasm of upper limb NOS
27449	B554.00	Malignant neoplasm of upper limb NOS
27483	B240.00	Malignant neoplasm of thymus
27509	BBP1.00	[M]Mesothelioma, malignant
27528	B303.00	Malignant neoplasm of ribs, sternum and clavicle
27540	B4A1000	Malignant neoplasm of renal calyces
27594	BBB1.11	[M]Warthin's tumour
27617	B45y000	Malignant neoplasm of overlapping lesion of vulva

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
27697	BB5Y.00	[M]Hypernephroid tumour
27715	B242.00	Malignant neoplasm of anterior mediastinum
27855	B140.00	Malignant neoplasm of rectosigmoid junction
27897	B143.00	Malignant neoplasm of anus unspecified
28069	B505.00	Malignant neoplasm of retina
28148	B540.00	Malignant neoplasm of adrenal gland
28163	B13z.00	Malignant neoplasm of colon NOS
28241	B496.00	Malignant neoplasm of ureteric orifice
28311	B41z.00	Malignant neoplasm of cervix uteri NOS
28451	B08z.00	Malignant neoplasm of hypopharynx NOS
28556	B32z.00	Malignant melanoma of skin NOS
28559	B055z00	Malignant neoplasm of palate NOS
28665	B07z.00	Malignant neoplasm of nasopharynx NOS
28727	B575000	Secondary malignant neoplasm of colon
28919	B521.00	Malignant neoplasm of cerebral meninges
28950	BBaz.00	[M]Miscellaneous tumour NOS
29160	B313000	Malignant neoplasm of connective and soft tissue of axilla
29282	BB30.00	[M]Basal cell tumour
29283	B2zy.00	Malignant neoplasm of other site of respiratory tract
29359	BBF0.00	[M]Soft tissue tumour, benign
29462	B4Az.00	Malignant neoplasm of kidney or urinary organs NOS
29789	B935.11	Histiocytic tumour NOS
29826	B342.00	Malignant neoplasm of upper-inner quadrant of female breast
29945	BBR4.00	[M]Malignant teratoma, trophoblastic
30165	B18y200	Malignant neoplasm of mesorectum
30402	B050.11	Malignant neoplasm of buccal mucosa
30537	F373.00	Polyneuropathy in malignant disease
30541	BB81.14	[M]Ovarian serous tumour
30543	B335200	Malignant neoplasm of skin of breast
30576	B333300	Malignant neoplasm of skin of forehead
30577	B336200	Malignant neoplasm of skin of fore-arm
30645	B333000	Malignant neoplasm of skin of cheek, external
30646	B6y..00	Malignant neoplasm lymphatic or haematopoietic tissue OS
30700	B10z.00	Malignant neoplasm of oesophagus NOS
30715	1J0A.00	Suspected kidney cancer
30747	B336.00	Malignant neoplasm of skin of upper limb and shoulder
31102	B49z.00	Malignant neoplasm of urinary bladder NOS
31170	BBCC.00	[M]Leydig cell tumour
31188	B224.00	Malignant neoplasm of lower lobe, bronchus or lung
31189	B7F0.11	Cerebral tumour - benign
31268	B223.00	Malignant neoplasm of middle lobe, bronchus or lung
31364	B050.00	Malignant neoplasm of cheek mucosa
31399	B555.00	Malignant neoplasm of lower limb NOS
31546	B341.00	Malignant neoplasm of central part of female breast
31573	B23..00	Malignant neoplasm of pleura
31574	BBb0.00	[M]Glioma, malignant

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
31608	B43y.00	Malignant neoplasm of other site of uterine body
31609	BBC4.00	[M]Granulosa cell tumour, malignant
31673	BBX1.12	[M]Osteoclastoma, malignant
31700	B222000	Malignant neoplasm of upper lobe bronchus
31726	BBgM.00	[M]Malignant lymphoma, small cleaved cell, diffuse
31755	G240.00	Secondary malignant hypertension
32022	B110.00	Malignant neoplasm of cardia of stomach
32024	B030.00	Malignant neoplasm of upper gum
32174	B202.00	Malignant neoplasm of maxillary sinus
32213	BB0A.00	[M]Malignant tumour, fusiform cell type
32294	BB5B500	[M]Glucagonoma, malignant
32362	B113.00	Malignant neoplasm of fundus of stomach
32372	B302100	Malignant neoplasm of thoracic vertebra
32442	BBW7.11	[M]Chondromatous giant cell tumour
32768	B325100	Malignant melanoma of breast
32919	SN5y011	Malignant hyperthermia due to anaesthesia
32955	B41y.00	Malignant neoplasm of other site of cervix
33271	B332200	Malignant neoplasm of pinna NEC
33333	B62..00	Other malignant neoplasm of lymphoid and histiocytic tissue
33344	B65z.00	Myeloid leukaemia NOS
33508	BB0z.00	[M]Unspecified tumour cell NOS
33617	B43z.00	Malignant neoplasm of body of uterus NOS
33636	BBQ7200	[M]Teratoma, malignant, NOS
33682	B337400	Malignant neoplasm of skin of lower leg
33833	B301.00	Malignant neoplasm of mandible
33843	B583.00	Secondary malignant neoplasm of brain and spinal cord
33869	BBgR.00	[M]Malignant lymphoma, large cell, diffuse NOS
33871	B122.00	Malignant neoplasm of ileum
33997	B332000	Malignant neoplasm of skin of auricle (ear)
34012	B08..00	Malignant neoplasm of hypopharynx
34089	B62y400	Malignant lymphoma NOS of lymph nodes of axilla and arm
34110	BB5R100	[M]Carcinoid tumour, malignant
34145	B58y600	Secondary malignant neoplasm of testis
34388	B17z.00	Malignant neoplasm of pancreas NOS
34409	B010000	Malignant neoplasm of base of tongue dorsal surface
34451	B31..00	Malignant neoplasm of connective and other soft tissue
34742	B23z.00	Malignant neoplasm of pleura NOS
34878	B308300	Malignant neoplasm of medial cuneiform
35039	B163.00	Malignant neoplasm, overlapping lesion of biliary tract
35071	BBQB.00	[M]Mixed germ cell tumour
35113	Byu9.00	[X]Malignant neoplasm of urinary tract
35180	Byu1.00	[X]Malignant neoplasm of digestive organs
35186	ByuC.00	[X]Malignant neoplasm of ill-defined, secondary and unspeci
35284	BBez.00	[M]Nerve sheath tumour NOS
35285	ByuA.00	[X]Malignant neoplasm of eye, brain and other parts of cent
35325	Byu2.00	[X]Malignant neoplasm of respiratory and intrathoracic orga

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
35357	B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
35364	B576000	Secondary malignant neoplasm of retroperitoneum
35535	B173.00	Malignant neoplasm of pancreatic duct
35795	B174.00	Malignant neoplasm of Islets of Langerhans
35963	B492.00	Malignant neoplasm of lateral wall of urinary bladder
35999	B582200	Secondary malignant neoplasm of skin of neck
36114	BBg1.00	[M]Malignant lymphoma NOS
36147	B153.00	Secondary malignant neoplasm of liver
36161	B012.00	Malignant neoplasm of tongue, tip and lateral border
36209	BBD6.00	[M]Carotid body tumour
36371	B225.00	Malignant neoplasm of overlapping lesion of bronchus & lung
36401	B587.00	Secondary malignant neoplasm of adrenal gland
36646	BBT..11	[M]Haemangiomatous tumours
36716	B04z.00	Malignant neoplasm of floor of mouth NOS
36731	B331000	Malignant neoplasm of canthus
36899	B327800	Malignant melanoma of toe
36949	B49y.00	Malignant neoplasm of other site of urinary bladder
37016	B33..14	Malignant neoplasm of sebaceous gland
37081	BBK3800	[M]Smooth muscle tumour NOS
37096	B015.00	Malignant neoplasm of tongue, junctional zone
37112	B6...11	Malignant neoplasm of histiocytic tissue
37128	BBp..00	[M]Mast cell tumours
37165	B334000	Malignant neoplasm of scalp
37328	B450.00	Malignant neoplasm of vagina
37477	BBe7.11	[M]Schwannoma, malignant
37516	B054.00	Malignant neoplasm of uvula
37553	B007.00	Malignant neoplasm of lip, unspecified
37590	B052.00	Malignant neoplasm of hard palate
37618	B551000	Malignant neoplasm of axilla NOS
37621	BBQ4.00	[M]Endodermal sinus tumour
37680	BBGF.00	[M]Fibrous histiocytoma, malignant
37724	B056.00	Malignant neoplasm of retromolar area
37805	B213100	Malignant neoplasm of cricoid cartilage
37810	B220z00	Malignant neoplasm of trachea NOS
37830	BBXz.00	[M]Giant cell tumour NOS
37842	B303000	Malignant neoplasm of rib
37859	B110z00	Malignant neoplasm of cardia of stomach NOS
37872	B327400	Malignant melanoma of lower leg
37916	B05y.00	Malignant neoplasm of other specified mouth parts
37940	B072000	Malignant neoplasm of pharyngeal recess
37969	B335100	Malignant neoplasm of skin of chest, excluding breast
38444	BB5R000	[M]Carcinoid tumour NOS
38475	B34yz00	Malignant neoplasm of other site of female breast NOS
38477	BBX0.00	[M]Giant cell tumour of bone NOS
38481	BBTK.00	[M]Epithelioid haemangioendothelioma, malignant
38488	B013z00	Malignant neoplasm of ventral tongue surface NOS

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
38510	B47z.00	Malignant neoplasm of testis NOS
38689	B325.00	Malignant melanoma of trunk (excluding scrotum)
38736	B5y..00	Malignant neoplasm of other and unspecified site OS
38862	B490.00	Malignant neoplasm of trigone of urinary bladder
38918	B583100	Secondary malignant neoplasm of spinal cord
38931	B4y..00	Malignant neoplasm of genitourinary organ OS
38938	B306z00	Malignant neoplasm of pelvis, sacrum or coccyx NOS
38961	B22y.00	Malignant neoplasm of other sites of bronchus or lung
38978	B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS
38979	BBC9.13	[M]Sertoli cell tumour
39007	BB81.13	[M]Ovarian papillary tumour
39027	ByuC000	[X]Malignant neoplasm of other specified sites
39084	B0z2.00	Malignant neoplasm of laryngopharynx
39088	B514.00	Malignant neoplasm of occipital lobe
39130	BB5R200	[M]Carcinoid tumour, argentaffin, NOS
39413	B18y500	Malignant neoplasm of pelvic peritoneum
39430	B0zz.00	Malignant neoplasm of lip, oral cavity and pharynx NOS
39554	B063.00	Malignant neoplasm of vallecula
39590	B206.00	Malignant neoplasm, overlapping lesion of accessory sinuses
39649	G220.00	Malignant hypertensive renal disease
39734	BBCD.00	[M]Hilar cell tumour
39870	B172.00	Malignant neoplasm of tail of pancreas
39878	B327300	Malignant melanoma of popliteal fossa area
39897	B081.00	Malignant neoplasm of pyriform sinus
39899	B542100	Malignant neoplasm of craniopharyngeal duct
39906	BBgE.00	[M]Malignant lymphoma, centrocytic
39923	B223100	Malignant neoplasm of middle lobe of lung
40014	B310100	Malignant neoplasm of soft tissue of face
40292	B053.00	Malignant neoplasm of soft palate
40415	BBU..11	[M]Lymphangiomatous tumours
40437	B50y.00	Malignant neoplasm of other specified site of eye
40443	B33..15	Malignant neoplasm of sweat gland
40492	BBe9.00	[M]Triton tumour, malignant
40557	B01z.00	Malignant neoplasm of tongue NOS
40592	Byu5.00	[X]Malignant neoplasm of mesothelial and soft tissue
40598	Byu7.00	[X]Malignant neoplasm of female genital organs
40608	ByuB.00	[X]Malignant neoplasm of thyroid and other endocrine glands
40671	Byu8.00	[X]Malignant neoplasm of male genital organs
40740	ByuD.00	[X]Malignant neoplasms of lymphoid, haematopoietic and rela
40749	Byu3.00	[X]Malignant neoplasm of bone and articular cartilage
40810	B171.00	Malignant neoplasm of body of pancreas
40814	B307200	Malignant neoplasm of tibia
40883	BB5h.00	[M]Adrenal cortical tumours
40966	B306300	Malignant neoplasm of sacral vertebra
41009	F501A00	Malignant otitis externa
41144	B582300	Secondary malignant neoplasm of skin of trunk

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Medcode	Read codes	Cancer terms
41215	B111100	Malignant neoplasm of pyloric canal of stomach
41274	BBZ..00	[M]Odontogenic tumours
41278	B323000	Malignant melanoma of external surface of cheek
41362	B101.00	Malignant neoplasm of thoracic oesophagus
41490	B327700	Malignant melanoma of foot
41515	ByuA100	[X]Malignant neoplasm/central nervous system, unspecified
41520	B51z.00	Malignant neoplasm of brain NOS
41523	B223000	Malignant neoplasm of middle lobe bronchus
41530	B01y.00	Malignant neoplasm of other sites of tongue
41571	B495.00	Malignant neoplasm of bladder neck
41695	BBba.00	[M]Primitive neuroectodermal tumour
41754	BBg7.00	[M]Malignant lymphoma, lymphoplasmacytoid type
41803	BBf..00	[M]Granular cell tumours and alveolar soft part sarcoma
41841	BBgB.00	[M]Malignant lymphoma, follicular centre cell NOS
41931	B550100	Malignant neoplasm of cheek NOS
41958	B331200	Malignant neoplasm of lower eyelid
42012	B494.00	Malignant neoplasm of posterior wall of urinary bladder
42023	B497.00	Malignant neoplasm of urachus
42070	B345.00	Malignant neoplasm of lower-outer quadrant of female breast
42153	B32y.00	Malignant melanoma of other specified skin site
42193	B115.00	Malignant neoplasm of lesser curve of stomach unspecified
42218	B55y.00	Malignant neoplasm of other specified sites
42416	B105.00	Malignant neoplasm of lower third of oesophagus
42426	B511.00	Malignant neoplasm of frontal lobe
42429	B33X.00	Malignant neoplasm overlapping lesion of skin
42460	B543.00	Malignant neoplasm of pineal gland
42566	B224z00	Malignant neoplasm of lower lobe, bronchus or lung NOS
42569	B2zz.00	Malignant neoplasm of respiratory tract NOS
42579	B62y300	Malignant lymphoma NOS of intra-abdominal lymph nodes
42707	B336100	Malignant neoplasm of skin of upper arm
42714	B327500	Malignant melanoma of ankle
42856	B200z00	Malignant neoplasm of nasal cavities NOS
43087	B331.00	Malignant neoplasm of eyelid including canthus
43111	B213.00	Malignant neoplasm of laryngeal cartilage
43122	B336000	Malignant neoplasm of skin of shoulder
43151	Byu3300	[X]Malignant neoplasm/bone+articular cartilage, unspecified
43189	BBED.00	[M]Precancerous melanosis NOS
43200	B06z.00	Malignant neoplasm of oropharynx NOS
43390	B12z.00	Malignant neoplasm of small intestine NOS
43392	B483.00	Malignant neoplasm of penis, part unspecified
43400	B03..00	Malignant neoplasm of gum
43431	B010.00	Malignant neoplasm of base of tongue
43435	B41yz00	Malignant neoplasm of other site of cervix NOS
43459	BBn..00	[M]Plasma cell tumours
43463	B325700	Malignant melanoma of back
43479	B121.00	Malignant neoplasm of jejunum

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Medcode	Read codes	Cancer terms
43548	B080.00	Malignant neoplasm of postcricoid region
43572	B114.00	Malignant neoplasm of body of stomach
43614	B30X.00	Malignant neoplasm/bones+articular cartilage/limb,unspfd
43619	B334100	Malignant neoplasm of skin of neck
43614	B30X.00	Malignant neoplasm/bones+articular cartilage/limb,unspfd
43642	B011.00	Malignant neoplasm of dorsal surface of tongue
43715	B325600	Malignant melanoma of umbilicus
43761	B451.00	Malignant neoplasm of labia majora
43781	B011z00	Malignant neoplasm of dorsum of tongue NOS
43930	B582000	Secondary malignant neoplasm of skin of head
43940	B431.00	Malignant neoplasm of isthmus of uterine body
44089	B517.00	Malignant neoplasm of brain stem
44108	B18..00	Malignant neoplasm of retroperitoneum and peritoneum
44134	1J0B.00	Suspected urothelial cancer
44139	B073.00	Malignant neoplasm of anterior wall of nasopharynx
44169	B222z00	Malignant neoplasm of upper lobe, bronchus or lung NOS
44207	BBn1.00	[M]Plasma cell tumour, benign
44217	BBL3.12	[M]Mixed tumour NOS
44267	B623.00	Malignant histiocytosis
44399	B150z00	Primary malignant neoplasm of liver NOS
44452	B300C00	Malignant neoplasm of vomer
44529	B575.00	Secondary malignant neoplasm of large intestine and rectum
44609	B306000	Malignant neoplasm of ilium
44615	B586.00	Secondary malignant neoplasm of ovary
44884	B4Ay.00	Malignant neoplasm of other urinary organs
44996	B491.00	Malignant neoplasm of dome of urinary bladder
45071	B314.00	Malignant neoplasm of connective and soft tissue of abdomen
45139	B323400	Malignant melanoma of external surface of nose
45154	B516.00	Malignant neoplasm of cerebellum
45189	BBZJ.00	[M]Squamous odontogenic tumour
45222	B343.00	Malignant neoplasm of lower-inner quadrant of female breast
45260	Byu9000	[X]Malignant neoplasm of urinary organ, unspecified
45262	Byu8200	[X]Malignant neoplasm of male genital organ, unspecified
45267	B55z.00	Malignant neoplasm of other and ill defined site NOS
45306	B324100	Malignant melanoma of neck
45364	BBX2.00	[M]Giant cell tumour of soft parts NOS
45408	B040.00	Malignant neoplasm of anterior portion of floor of mouth
45490	B430z00	Malignant neoplasm of corpus uteri NOS
45573	BB5Rz00	[M]Carcinoid tumours NOS
45667	B501.00	Malignant neoplasm of orbit
45755	B326200	Malignant melanoma of fore-arm
45760	B325z00	Malignant melanoma of trunk, excluding scrotum, NOS
45766	Byu1200	[X]Malignant neoplasm of intestinal tract, part unspecified
45793	B430300	Malignant neoplasm of myometrium of corpus uteri
45814	BB5C011	[M]G cell tumour NOS
45824	B58y900	Secondary malignant neoplasm of tongue

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Medcode	Read codes	Cancer terms
45922	B508.00	Malignant neoplasm, overlapping lesion of eye and adnexa
45969	BBDC.00	[M]Glomus tumour
45986	B041.00	Malignant neoplasm of lateral portion of floor of mouth
46008	B333z00	Malignant neoplasm skin other and unspec part of face NOS
46041	F282.11	Pseudotumour cerebri
46153	B443.00	Malignant neoplasm of parametrium
46159	B142000	Malignant neoplasm of cloacogenic zone
46255	B327.00	Malignant melanoma of lower limb and hip
46548	B071100	Malignant neoplasm of pharyngeal tonsil
46613	B18y.00	Malignant neoplasm of specified parts of peritoneum
46728	B064.00	Malignant neoplasm of anterior epiglottis
46789	B515000	Malignant neoplasm of choroid plexus
46792	B512.00	Malignant neoplasm of temporal lobe
46877	BBgL.00	[M]Malignant lymphoma, small lymphocytic NOS
46905	B545200	Malignant neoplasm of coccygeal body
46931	BBg4.00	[M]Malignant lymphoma, stem cell type
46939	B302000	Malignant neoplasm of cervical vertebra
47094	B323200	Malignant melanoma of eyebrow
47205	B017.00	Malignant overlapping lesion of tongue
47252	B323.00	Malignant melanoma of other and unspecified parts of face
47286	B551.00	Malignant neoplasm of thorax
47556	B512z00	Malignant neoplasm of temporal lobe NOS
47668	B48y100	Malignant neoplasm of tunica vaginalis
47734	BBP5.00	[M]Epithelioid mesothelioma, malignant
47767	B486.00	Malignant neoplasm of scrotum
47801	B49y000	Malignant neoplasm, overlapping lesion of bladder
47810	B59..00	Malignant neoplasm of unspecified site
47810	B59..00	Malignant neoplasm of unspecified site
47840	B545100	Malignant neoplasm of aortic body
47862	B213300	Malignant neoplasm of thyroid cartilage
47899	B451000	Malignant neoplasm of greater vestibular (Bartholin's) gland
48073	B510000	Malignant neoplasm of basal ganglia
48231	B13y.00	Malignant neoplasm of other specified sites of colon
48237	B111000	Malignant neoplasm of prepylorus of stomach
48479	F456400	Glaucoma due to ocular tumour or cyst
48517	B310200	Malignant neoplasm of soft tissue of neck
48253	BBg8.00	[M]Malignant lymphoma, immunoblastic type
48342	1J0J.00	Suspected gynaecological cancer
48519	B065.00	Malignant neoplasm of junctional region of epiglottis
48537	B17y.00	Malignant neoplasm of other specified sites of pancreas
48743	B482.00	Malignant neoplasm of body of penis
48809	B35zz00	Malignant neoplasm of male breast NOS
48820	B410.00	Malignant neoplasm of endocervix
48828	B582500	Secondary malignant neoplasm of skin of hip and leg
48957	BBC5.00	[M]Granulosa cell-theca cell tumour
49033	A220.11	Malignant pustule

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Medcode	Read codes	Cancer terms
49054	B304000	Malignant neoplasm of scapula
49131	BBg0.00	[M]Lymphomatous tumour, benign
49132	B517100	Malignant neoplasm of medulla oblongata
49145	B58y700	Secondary malignant neoplasm of penis
49148	B347.00	Malignant neoplasm, overlapping lesion of breast
49286	BBCC011	[M]Interstitial cell tumour, benign
49292	Byu1300	[X]Malignant neoplsm/ill-defin sites within digestive system
49301	B6z..00	Malignant neoplasm lymphatic or haematopoietic tissue NOS
49341	4D56.00	Pleural fluid: malignant cells
49360	B031.00	Malignant neoplasm of lower gum
49400	B430211	Malignant neoplasm of endometrium
49403	B333100	Malignant neoplasm of skin of chin
49463	B310400	Malignant neoplasm of tarsus of eyelid
49482	F396200	Myopathy due to malignant disease
49491	B303100	Malignant neoplasm of sternum
49701	B302z00	Malignant neoplasm of vertebral column NOS
49714	B523.00	Malignant neoplasm of spinal meninges
49758	B0zy.00	Malignant neoplasm of other sites lip, oral cavity, pharynx
49811	BBL6.00	[M]Mesodermal mixed tumour
49814	B325000	Malignant melanoma of axilla
49828	B441.00	Malignant neoplasm of fallopian tube
49875	B52X.00	Malignant neoplasm of meninges, unspecified
49900	BB5y200	[M]Klatskin's tumour
50035	B545.00	Malignant neoplasm of aortic body and other paraganglia
50152	B306500	Malignant sacral teratoma
50157	G210.00	Malignant hypertensive heart disease
50222	B311000	Malignant neoplasm of connective and soft tissue of shoulder
50285	B410z00	Malignant neoplasm of endocervix NOS
50289	B241z00	Malignant neoplasm of heart NOS
50292	Byu2500	[X]Malignant neoplasm of mediastinum, part unspecified
50296	B000100	Malignant neoplasm of upper lip, lipstick area
50297	B411.00	Malignant neoplasm of exocervix
50298	B300500	Malignant neoplasm of orbital bone
50299	B300900	Malignant neoplasm of zygomatic bone
50402	B307100	Malignant neoplasm of fibula
50475	B02z.00	Malignant neoplasm of major salivary gland NOS
50505	B326000	Malignant melanoma of shoulder
50519	BBCF.00	[M]Adrenal rest tumour
50579	B214.00	Malignant neoplasm, overlapping lesion of larynx
50681	B480.00	Malignant neoplasm of prepuce (foreskin)
50696	B62y100	Malignant lymphoma NOS of lymph nodes of head, face and neck
50753	BB5H.11	[M]Turban tumour
50777	B524600	Malignant neoplasm,overlap lesion periph nerve & auton ns
50789	B103.00	Malignant neoplasm of upper third of oesophagus
50974	B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
51115	B522.00	Malignant neoplasm of spinal cord

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
51209	B325800	Malignant melanoma of chest wall
51237	B303z00	Malignant neoplasm of rib, sternum and clavicle NOS
51255	B1zz.00	Malignant neoplasm of digestive tract and peritoneum NOS
51352	B592.00	Malignant neoplasms of independent (474) multiple sites
51353	BBE1000	[M]Malignant melanoma, regressing
51551	B571.00	Secondary malignant neoplasm of mediastinum
51680	BBgV.00	[M]Malignant lymphoma, small cell, noncleaved, diffuse
51690	B117.00	Malignant neoplasm, overlapping lesion of stomach
51786	B021.00	Malignant neoplasm of submandibular gland
51795	B545000	Malignant neoplasm of glomus jugulare
51818	B550300	Malignant neoplasm of jaw NOS
51873	B327100	Malignant melanoma of thigh
51921	B306200	Malignant neoplasm of pubis
51926	B062000	Malignant neoplasm of faucial pillar
51965	B315.00	Malignant neoplasm of connective and soft tissue of pelvis
52029	ByuC800	[X]Malignant neoplasm without specification of site
52178	BBTL.00	[M]Intravascular bronchial alveolar tumour
52266	BB5a011	[M]Grawitz tumour
52316	B553.00	Malignant neoplasm of pelvis
52493	BBQ7213	[M]Teratoblastoma, malignant
52511	B515.00	Malignant neoplasm of cerebral ventricles
52537	B161100	Malignant neoplasm of hepatic duct
52570	B487.00	Malignant neoplasm, overlapping lesion of penis
52594	B4z..00	Malignant neoplasm of genitourinary organ NOS
52963	BBC3000	[M]Juvenile granulosa cell tumour
53103	B410100	Malignant neoplasm of endocervical gland
53141	L241.00	Tumour of uterine body in pregnancy/childbirth/puerperium
53369	B327900	Malignant melanoma of great toe
53515	B332.00	Malignant neoplasm skin of ear and external auricular canal
53528	B581200	Secondary malignant neoplasm of urethra
53591	B10y.00	Malignant neoplasm of other specified part of oesophagus
53594	B300000	Malignant neoplasm of ethmoid bone
53599	B300100	Malignant neoplasm of frontal bone
53629	B325200	Malignant melanoma of buttock
53694	BB85111	[M]Krukenberg tumour
53884	B060z00	Malignant neoplasm tonsil NOS
53910	B453.00	Malignant neoplasm of clitoris
54103	B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts
54120	B584.00	Secondary malignant neoplasm of other part of nervous system
54133	B510z00	Malignant neoplasm of cerebrum NOS
54134	B223z00	Malignant neoplasm of middle lobe, bronchus or lung NOS
54171	B104.00	Malignant neoplasm of middle third of oesophagus
54184	B4A1z00	Malignant neoplasm of renal pelvis NOS
54186	B313100	Malignant neoplasm of diaphragm
54202	B35z.00	Malignant neoplasm of other site of male breast
54222	B312400	Malignant neoplasm of connective and soft tissue of foot

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
54234	B334.00	Malignant neoplasm of scalp and skin of neck
54253	ByuC700	[X]Secondary malignant neoplasm of other specified sites
54267	B59z.00	Malignant neoplasm of unspecified site NOS
54267	B59z.00	Malignant neoplasm of unspecified site NOS
54305	B327200	Malignant melanoma of knee
54352	B336300	Malignant neoplasm of skin of hand
54493	B303500	Malignant neoplasm of xiphoid process
54494	B350.00	Malignant neoplasm of nipple and areola of male breast
54613	B201200	Malignant neoplasm of tympanic antrum
54631	B306.00	Malignant neoplasm of pelvic bones, sacrum and coccyx
54632	B321.00	Malignant melanoma of eyelid including canthus
54636	B203.00	Malignant neoplasm of ethmoid sinus
54654	BBC0.00	[M]Sex cord-stromal tumour
54679	B594.00	Secondary malignant neoplasm of unknown site
54691	B302200	Malignant neoplasm of lumbar vertebra
54747	B300600	Malignant neoplasm of parietal bone
54956	B50z.00	Malignant neoplasm of eye NOS
54965	B312200	Malig neop connective and soft tissue of popliteal space
55015	B05z.00	Malignant neoplasm of mouth NOS
55019	B11y.00	Malignant neoplasm of other specified site of stomach
55066	B062.00	Malignant neoplasm of tonsillar pillar
55090	B58y100	Secondary malignant neoplasm of uterus
55098	B550000	Malignant neoplasm of head NOS
55101	B553z00	Malignant neoplasm of pelvis NOS
55116	BBFz.00	[M]Soft tissue tumour or sarcoma NOS
55246	B20z.00	Malignant neoplasm of accessory sinus NOS
55292	B326z00	Malignant melanoma of upper limb or shoulder NOS
55374	B215.00	Malignant neoplasm of epiglottis NOS
55434	B116.00	Malignant neoplasm of greater curve of stomach unspecified
55468	BB5R600	[M]Mucocarcinoid tumour, malignant
55550	B331100	Malignant neoplasm of upper eyelid
55588	Byu7300	[X]Malignant neoplasm of female genital organ, unspecified
55595	B300700	Malignant neoplasm of sphenoid bone
55630	B07y.00	Malignant neoplasm of other specified site of nasopharynx
55670	B333200	Malignant neoplasm of skin of eyebrow
55675	B717011	Endocrine tumour of pancreas
55833	BBZ1.00	[M]Odontogenic tumour NOS
55881	B324000	Malignant melanoma of scalp
55946	B574000	Secondary malignant neoplasm of duodenum
55946	B574000	Secondary malignant neoplasm of duodenum
55953	B300400	Malignant neoplasm of occipital bone
56121	Byu4300	[X]Malignant neoplasm of skin, unspecified
56345	B57y.00	Secondary malignant neoplasm of other digestive organ
56355	B066.00	Malignant neoplasm of lateral wall of oropharynx
56490	B52z.00	Malignant neoplasm of nervous system NOS
56513	B307000	Malignant neoplasm of femur

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Medcode	Read codes	Cancer terms
56524	N332500	Brown tumour of hyperparathyroidism
56709	B04y.00	Malignant neoplasm of other sites of floor of mouth
56715	B34y.00	Malignant neoplasm of other site of female breast
56718	B500z00	Malignant neoplasm of eyeball NOS
56794	BB5R800	[M]Adenocarcinoid tumour
56918	B1zy.00	Malignant neoplasm other spec digestive tract and peritoneum
56925	Byu4000	[X]Malignant melanoma of other+unspecified parts of face
56954	B337200	Malignant neoplasm of skin of knee
57047	B544.00	Malignant neoplasm of carotid body
57177	SN5y100	Malignant hypothermia due to anaesthetic
57184	Byu4200	[X]Oth malignant neoplasm/skin of oth+unspecfd parts of face
57191	Byu8000	[X]Malignant neoplasm/other specified male genital organs
57235	B410000	Malignant neoplasm of endocervical canal
57248	B082.00	Malignant neoplasm aryepiglottic fold, hypopharyngeal aspect
57260	B322.00	Malignant melanoma of ear and external auricular canal
57336	BB16.00	[M]Epithelioma, malignant
57427	B62y000	Malignant lymphoma NOS of unspecified site
57442	B337.00	Malignant neoplasm of skin of lower limb and hip
57446	B335.00	Malignant neoplasm of skin of trunk, excluding scrotum
57481	ByuC300	[X]Secondary malignant neoplasm/oth+unspc respiratory organs
57482	B311200	Malignant neoplasm of connective and soft tissue of fore-arm
57601	BBJD.11	[M]Brown fat tumour
57719	B41y100	Malignant neoplasm of squamocolumnar junction of cervix
57756	Byu7100	[X]Malignant neoplasm/other specified female genital organs
57839	1J0K.00	Suspected pancreatic cancer
57854	B553000	Malignant neoplasm of inguinal region NOS
57988	B305000	Malignant neoplasm of carpal bone - scaphoid
58061	B452.00	Malignant neoplasm of labia minora
58088	B151400	Malignant neoplasm of intrahepatic gall duct
58094	B412.00	Malignant neoplasm, overlapping lesion of cervix uteri
58121	B014.00	Malignant neoplasm of anterior 2/3 of tongue unspecified
58601	B337100	Malignant neoplasm of skin of thigh
58835	BBE1100	[M]Desmoplastic melanoma, malignant
58871	B623z00	Malignant histiocytosis NOS
58902	BBcA.00	[M]Olfactory neurogenic tumour
58903	B550z00	Malignant neoplasm of head, neck and face NOS
58949	B308D00	Malignant neoplasm of phalanges of foot
58958	B323500	Malignant melanoma of temple
58962	B62x500	Malignant immunoproliferative small intestinal disease
58973	Byu0.00	[X]Malignant neoplasm of lip, oral cavity and pharynx
58976	BBT..00	[M]Blood vessel tumours
59004	B072.00	Malignant neoplasm of lateral wall of nasopharynx
59036	B300.00	Malignant neoplasm of bones of skull and face
59041	B500000	Malignant neoplasm of ciliary body
59061	B322000	Malignant melanoma of auricle (ear)
59092	B111z00	Malignant neoplasm of pylorus of stomach NOS

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Medcode	Read codes	Cancer terms
59097	B431000	Malignant neoplasm of lower uterine segment
59100	BB70.00	[M]Mucoepidermoid tumour
59152	B315200	Malignant neoplasm of connective and soft tissue of perineum
59170	B51y000	Malignant neoplasm of corpus callosum
59223	B306100	Malignant neoplasm of ischium
59251	BBM9.00	[M]Cystosarcoma phyllodes, malignant
59274	BBZP.00	[M]Calcifying epithelial odontogenic tumour
59286	B4Ay000	Malignant neoplasm of overlapping lesion of urinary organs
59362	B451z00	Malignant neoplasm of labia majora NOS
59375	B583z00	Secondary malignant neoplasm of brain or spinal cord NOS
59381	B500100	Malignant neoplasm of iris
59382	B310000	Malignant neoplasm of soft tissue of head
59383	G240000	Secondary malignant renovascular hypertension
59388	B18y100	Malignant neoplasm of mesocaecum
59415	BBB6100	[M]Thymoma, malignant
59520	B300200	Malignant neoplasm of malar bone
59823	B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct
59831	B340z00	Malignant neoplasm of nipple or areola of female breast NOS
59995	BBCE.00	[M]Lipid cell tumour of ovary
60035	B310300	Malignant neoplasm of cartilage of ear
60052	B55yz00	Malignant neoplasm of specified site NOS
60092	B62y700	Malignant lymphoma NOS of spleen
60134	B581000	Secondary malignant neoplasm of ureter
60162	Byu5A00	[X]Malignant neoplasm overlapping lesion of skin
60275	BBgJ.00	[M]Malignant lymphoma, centroblastic type NOS
60312	B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct
60335	B58y400	Secondary malignant neoplasm of vulva
60403	B303300	Malignant neoplasm of costal cartilage
60526	B336z00	Malignant neoplasm of skin of upper limb or shoulder NOS
60772	B450z00	Malignant neoplasm of vagina NOS
61064	B24X.00	Malignant neoplasm of mediastinum, part unspecified
61115	BBC0000	[M]Sex cord tumour with annular tubules
61194	B337z00	Malignant neoplasm of skin of lower limb or hip NOS
61246	B327600	Malignant melanoma of heel
61390	B540000	Malignant neoplasm of adrenal cortex
61399	B510100	Malignant neoplasm of cerebral cortex
61510	B062200	Malignant neoplasm of palatoglossal arch
61542	BBQ7400	[M]Malignant teratoma, undifferentiated type
61555	B180z00	Malignant neoplasm of retroperitoneum NOS
61643	B151z00	Malignant neoplasm of intrahepatic bile ducts NOS
61692	B004.00	Malignant neoplasm of lip unspecified, inner aspect
61695	B100.00	Malignant neoplasm of cervical oesophagus
61716	B524100	Malignant neoplasm of peripheral nerve,upp limb,incl should
61741	B304200	Malignant neoplasm of humerus
62080	B332100	Malignant neoplasm of skin of external auditory meatus
62088	BBEG.00	[M]Malignant melanoma in Hutchinson's melanotic freckle

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Medcode	Read codes	Cancer terms
62104	B300800	Malignant neoplasm of temporal bone
62126	B510500	Malignant neoplasm of thalamus
62182	B200300	Malignant neoplasm of vestibule of nose
62256	BB5hz00	[M]Adrenal cortical tumours NOS
62305	B335800	Malignant neoplasm of skin of buttock
62437	B62x400	Malignant reticulosis
62556	B24..00	Malignant neoplasm of thymus, heart and mediastinum
62584	B573.00	Secondary malignant neoplasm of other respiratory organs
62630	B307z00	Malignant neoplasm of long bones of leg NOS
62761	B200200	Malignant neoplasm of septum of nose
62828	B581z00	Secondary malignant neoplasm of other urinary organ NOS
62840	B013.00	Malignant neoplasm of ventral surface of tongue
62881	BBTz.00	[M]Blood vessel tumour NOS
62909	B575100	Secondary malignant neoplasm of rectum
62944	BBCC000	[M]Leydig cell tumour, benign
62951	5A15.00	Bone tumour/metast.irradiat.
63104	B501z00	Malignant neoplasm of orbit NOS
63105	B62y500	Malignant lymphoma NOS of lymph node inguinal region and leg
63224	B48z.00	Malignant neoplasm of penis and other male genital organ NOS
63239	BBm1.00	[M]Malignant histiocytosis
63300	Byu3200	[X]Malignant neoplasm/overlap lesion/bone+articulr cartilage
63331	B485.00	Malignant neoplasm of spermatic cord
63376	F402100	Malignant myopia
63430	B241000	Malignant neoplasm of endocardium
63460	B213000	Malignant neoplasm of arytenoid cartilage
63470	B102.00	Malignant neoplasm of abdominal oesophagus
63568	B524000	Malignant neoplasm of peripheral nerves of head, face & neck
63574	BBEC.00	[M]Malignant melanoma in junctional naevus
63598	ByuE.00	[X]Malignant neoplasms/independent (474) multiple sites
63657	B503.00	Malignant neoplasm of conjunctiva
63695	B524300	Malignant neoplasm of peripheral nerve of thorax
63699	BBk0.00	[M]Malignant lymphoma, nodular NOS
63896	B582400	Secondary malignant neoplasm of skin of shoulder and arm
63925	ByuA200	[X]Malignant neoplasm of meninges, unspecified
63979	B013100	Malignant neoplasm of frenulum linguae
63988	B311500	Malignant neoplasm of connective and soft tissue of thumb
63994	BBgS.00	[M]Malignant lymphoma, large cell, cleaved, diffuse
63995	B123.00	Malignant neoplasm of Meckel's diverticulum
63997	B326500	Malignant melanoma of thumb
64068	BBnz.00	[M]Plasma cell tumour NOS
64106	B18yz00	Malignant neoplasm of specified parts of peritoneum NOS
64270	B337500	Malignant neoplasm of skin of ankle
64309	ByuB100	[X]Malignant neoplasm of endocrine gland, unspecified
64314	BBa..00	[M]Miscellaneous tumours
64327	B327z00	Malignant melanoma of lower limb or hip NOS
64345	B311100	Malignant neoplasm of connective and soft tissue, upper arm

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Medcode	Read codes	Cancer terms
64406	B336500	Malignant neoplasm of skin of thumb
64462	B083.00	Malignant neoplasm of posterior pharynx
64497	Byu7000	[X]Malignant neoplasm of uterine adnexa, unspecified
64516	B18y400	Malignant neoplasm of parietal peritoneum
64557	B517000	Malignant neoplasm of cerebral peduncle
64602	B470.00	Malignant neoplasm of undescended testis
64680	B574.00	Secondary malignant neoplasm of small intestine and duodenum
64810	B551z00	Malignant neoplasm of thorax NOS
64817	B502.00	Malignant neoplasm of lacrimal gland
64848	B304400	Malignant neoplasm of ulna
64874	BBa4.00	[M]Melanotic neuroectodermal tumour
64897	ByuE000	[X]Malignant neoplasms/independent(474)multiple sites
64971	B520000	Malignant neoplasm of olfactory bulb
65106	B44z.00	Malignant neoplasm of uterine adnexa NOS
65124	B151000	Malignant neoplasm of interlobular bile ducts
65159	B180100	Malignant neoplasm of perinephric tissue
65164	B326.00	Malignant melanoma of upper limb and shoulder
65172	4C54.00	Bone marrow: tumour cells
65215	B205.00	Malignant neoplasm of sphenoidal sinus
65241	B51y200	Malignant neoplasm, overlapping lesion of brain
65253	B560300	Secondary and unspec malignant neoplasm occipital lymph node
65312	B11y000	Malignant neoplasm of anterior wall of stomach NEC
65357	B507100	Malignant neoplasm of nasolacrimal duct
65372	B11yz00	Malignant neoplasm of other specified site of stomach NOS
65434	B62z.00	Malignant neoplasms of lymphoid and histiocytic tissue NOS
65460	B1z1.00	Malignant neoplasm of spleen NEC
65490	B58y411	Secondary cancer of the vulva
65599	B520200	Malignant neoplasm of acoustic nerve
65605	B241200	Malignant neoplasm of myocardium
65625	B324.00	Malignant melanoma of scalp and neck
65642	B623300	Malignant histiocytosis of intra-abdominal lymph nodes
65782	B337800	Malignant neoplasm of skin of toe
65861	BBQ9.00	[M]Dermoid cyst with malignant transformation
66163	ByuC200	[X]2ndry+unspcf malignant neoplasm lymph nodes/multi regions
66166	B124.00	Malignant neoplasm, overlapping lesion of small intestine
66270	B000000	Malignant neoplasm of upper lip, external
66270	B000000	Malignant neoplasm of upper lip, external
66319	B335500	Malignant neoplasm of skin of groin
66384	B001000	Malignant neoplasm of lower lip, external
66422	B074.00	Malignant neoplasm, overlapping lesion of nasopharynx
66444	Byu2100	[X]Malignant neoplasm/overlap lesion/heart,mediastinm+pleura
66447	B335A00	Malignant neoplasm of skin of scapular region
66502	BBYz.00	[M]Miscellaneous bone tumour NOS
66607	BBL4.00	[M]Mixed tumour, malignant, NOS
66608	L241300	Tumour of uterine body complicating a/n care, baby not deliv
66639	B303200	Malignant neoplasm of clavicle

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Medcode	Read codes	Cancer terms
66646	B26..00	Malignant neoplasm, overlap lesion of resp & intrathor orgs
66750	B24z.00	Malignant neoplasm of heart, thymus and mediastinum NOS
66775	B560100	Secondary and unspec malignant neoplasm mastoid lymph nodes
66908	B306400	Malignant neoplasm of coccygeal vertebra
67018	BBD5.00	[M]Aortic body tumour
67107	B230.00	Malignant neoplasm of parietal pleura
67211	B523z00	Malignant neoplasm of spinal meninges NOS
67217	B55y100	Malignant neoplasm of trunk NOS
67232	G230.00	Malignant hypertensive heart and renal disease
67236	B512000	Malignant neoplasm of hippocampus
67248	5A12.00	Thyroid tumour/metast irradiat
67323	B06y.00	Malignant neoplasm of oropharynx, other specified sites
67339	BBp2.00	[M]Malignant mastocytosis
67354	BB61100	[M]Sweat gland tumour NOS
67396	B576.00	Secondary malig neop of retroperitoneum and peritoneum
67446	B001.00	Malignant neoplasm of lower lip, vermilion border
67451	B30W.00	Malignant neoplasm/overlap lesion/bone+articulr cartilage
67497	B106.00	Malignant neoplasm, overlapping lesion of oesophagus
67504	B003000	Malignant neoplasm of lower lip, buccal aspect
67575	A788W00	HIV disease resulting in unspecified malignant neoplasm
67748	B335400	Malignant neoplasm of skin of umbilicus
67763	B303400	Malignant neoplasm of costo-vertebral joint
67806	B323z00	Malignant melanoma of face NOS
67884	B350100	Malignant neoplasm of areola of male breast
67914	B337900	Malignant neoplasm of skin of great toe
67949	B48y.00	Malignant neoplasm of other male genital organ
68027	ByuA000	[X]Malignant neoplasm/other and unspecified cranial nerves
68055	B307.00	Malignant neoplasm of long bones of leg
68133	B323300	Malignant melanoma of forehead
68155	B430100	Malignant neoplasm of fundus of corpus uteri
68161	B48y000	Malignant neoplasm of seminal vesicle
68197	B337300	Malignant neoplasm of skin of popliteal fossa area
68236	B550.00	Malignant neoplasm of head, neck and face
68332	ByuC600	[X]2ndry malignant neoplasm/oth+unspec parts/nervous system
68399	B004200	Malignant neoplasm of lip unspecified, mucosa
68447	BBEV.00	[M]Blue naevus, malignant
68480	B350000	Malignant neoplasm of nipple of male breast
68641	B517z00	Malignant neoplasm of brain stem NOS
68679	BB1H.00	[M]Tumourlet
68787	B55y000	Malignant neoplasm of back NOS
68824	B48y200	Malignant neoplasm, overlapping lesion male genital orgs
68956	BBX1.00	[M]Giant cell tumour of bone, malignant
68964	BBgA.00	[M]Malignant lymphoma, centroblastic-centrocytic, diffuse
69104	B305100	Malignant neoplasm of carpal bone - lunate
69146	B300z00	Malignant neoplasm of bones of skull and face NOS
69210	BB5R611	[M]Goblet cell tumour

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Medcode	Read codes	Cancer terms
69301	BBg5.00	[M]Malignant lymphoma, convoluted cell type NOS
69421	BBDz.00	[M]Paraganglioma or glomus tumour NOS
69497	B623000	Malignant histiocytosis of unspecified site
69671	B010.11	Malignant neoplasm of posterior third of tongue
69761	B00zz00	Malignant neoplasm of lip, vermilion border NOS
69821	B18y600	Malignant neoplasm of the pouch of Douglas
69927	B308800	Malignant neoplasm of first metatarsal bone
69951	B055100	Malignant neoplasm of roof of mouth
69980	BBgC.00	[M]Malignant lymphoma, lymphocytic, well differentiated NOS
69981	BBe7.00	[M]Neurilemmoma, malignant
70104	B521z00	Malignant neoplasm of cerebral meninges NOS
70126	B520100	Malignant neoplasm of optic nerve
70380	B335000	Malignant neoplasm of skin of axillary fold
70383	BBM0100	[M]Brenner tumour, malignant
70463	B315000	Malignant neoplasm of connective and soft tissue of buttock
70587	B337700	Malignant neoplasm of skin of foot
70637	B320.00	Malignant melanoma of lip
70696	B02y.00	Malignant neoplasm of other major salivary glands
70729	B431z00	Malignant neoplasm of isthmus of uterine body NOS
70736	B58y300	Secondary malignant neoplasm of vagina
70740	BBm1.11	[M]Malignant reticulosis
70819	B055.00	Malignant neoplasm of palate unspecified
70824	B540z00	Malignant neoplasm of adrenal gland NOS
70842	B627100	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma
70928	B022.00	Malignant neoplasm of sublingual gland
70942	B510400	Malignant neoplasm of hypothalamus
70988	B337000	Malignant neoplasm of skin of hip
71117	BBg3.00	[M]Malignant lymphoma, undifferentiated cell type NOS
71136	B323100	Malignant melanoma of chin
71139	B51y.00	Malignant neoplasm of other parts of brain
71147	B003.00	Malignant neoplasm of lower lip, inner aspect
71204	B200000	Malignant neoplasm of cartilage of nose
71262	B62y600	Malignant lymphoma NOS of intrapelvic lymph nodes
71301	BBQA100	[M]Struma ovarii, malignant
71481	BBU..00	[M]Lymphatic vessel tumours
71490	BBM0000	[M]Brenner tumour, borderline malignancy
71584	B507.00	Malignant neoplasm of lacrimal duct
71619	BBgT.00	[M]Malignant lymphoma, large cell, noncleaved, diffuse
71652	BBgP.00	[M]Malignant lymphoma, mixed small and large cell, diffuse
71810	B304.00	Malignant neoplasm of scapula and long bones of upper arm
71946	B201300	Malignant neoplasm of mastoid air cells
72127	B484.00	Malignant neoplasm of epididymis
72174	B4A4.00	Malignant neoplasm of paraurethral glands
72196	BBgG.00	[M]Malignant lymphoma, lymphocytic, poorly different NOS
72212	B308200	Malignant neoplasm of calcaneum
72215	L241z00	Uterine body tumour in pregnancy/childbirth/puerperium NOS

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Medcode	Read codes	Cancer terms
72230	L241100	Tumour of uterine body - baby delivered
72440	BBA1.00	[M]Acinar cell tumour
72443	BBZ2.00	[M]Odontogenic tumour, malignant
72445	B161000	Malignant neoplasm of cystic duct
72464	B305.12	Malignant neoplasm of metacarpal bones
72522	B313200	Malignant neoplasm of great vessels
72668	G210100	Malignant hypertensive heart disease with CCF
72684	BB81L00	[M]Papillary cystic tumour
72723	B430000	Malignant neoplasm of cornu of corpus uteri
72725	B62y200	Malignant lymphoma NOS of intrathoracic lymph nodes
73023	BBa4.13	[M]Retinal angle tumour
73213	B581.00	Secondary malignant neoplasm of other urinary organs
73293	G240z00	Secondary malignant hypertension NOS
73296	Byu3100	[X]Malignant neoplasm/bones+articular cartilage/limb,unspfd
73439	B064z00	Malignant neoplasm of anterior epiglottis NOS
73510	B550500	Malignant neoplasm of supraclavicular fossa NOS
73530	B305.00	Malignant neoplasm of hand bones
73536	B327000	Malignant melanoma of hip
73556	B305z00	Malignant neoplasm of hand bones NOS
73614	B004000	Malignant neoplasm of lip unspecified, buccal aspect
73616	B58y200	Secondary malignant neoplasm of cervix uteri
73623	BBCCz00	[M]Leydig cell tumour NOS
73744	B322z00	Malignant melanoma of ear and external auricular canal NOS
73760	B334z00	Malignant neoplasm of scalp or skin of neck NOS
73962	B000.00	Malignant neoplasm of upper lip, vermilion border
73988	B524500	Malignant neoplasm of peripheral nerve of pelvis
73992	B504.00	Malignant neoplasm of cornea
74896	B161z00	Malignant neoplasm of extrahepatic bile ducts NOS
85190	F562100	Malignant positional vertigo
86046	B524400	Malignant neoplasm of peripheral nerve of abdomen
86812	B305D00	Malignant neoplasm of phalanges of hand
86820	BBP7.00	[M]Mesothelioma, biphasic type, malignant
86996	B501000	Malignant neoplasm of connective tissue of orbit
86997	Byu2400	[X]Malignant neoplasm/ill-defined sites within resp system
87003	BBLC100	[M]Mesenchymoma, malignant
87113	B54X.00	Malignant neoplasm-pluriglandular involvement,unspecified
88022	ByuC400	[X]Secondary malignant neoplasm/oth+unspcfd digestive organs
88144	B52y.00	Malignant neoplasm of other specified part of nervous system
88362	B08y.00	Malignant neoplasm of other specified hypopharyngeal site
88593	BBR6.00	[M]Placental site trophoblastic tumour
89258	B524200	Malignant neoplasm of peripheral nerve of low limb, incl hip
89593	B151200	Malignant neoplasm of intrahepatic biliary passages
89657	B626z00	Malignant mast cell tumour NOS
89657	B626z00	Malignant mast cell tumour NOS
89909	B003200	Malignant neoplasm of lower lip, mucosa
89916	B553100	Malignant neoplasm of presacral region

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
90124	B067.00	Malignant neoplasm of posterior wall of oropharynx
90290	B18y700	Malignant neoplasm of mesentery
90610	B002300	Malignant neoplasm of upper lip, oral aspect
90659	B54y.00	Malignant neoplasm of other specified endocrine gland
91035	B010z00	Malignant neoplasm of fixed part of tongue NOS
91037	B06yz00	Malignant neoplasm of other specified site of oropharynx NOS
91240	B517300	Malignant neoplasm of pons
91457	Byu5900	[X]Malignant neoplasm/connective + soft tissue,unspecified
91509	B471z00	Malignant neoplasm of descended testis NOS
91586	B311400	Malignant neoplasm of connective and soft tissue of finger
91843	B003100	Malignant neoplasm of lower lip, frenulum
91895	B064100	Malignant neoplasm of glossoepiglottic fold
92275	BBC0.11	[M]Gonadal stromal tumour
92329	B48yz00	Malignant neoplasm of other male genital organ NOS
92371	B304300	Malignant neoplasm of radius
92382	B308B00	Malignant neoplasm of fourth metatarsal bone
92385	BBpz.00	[M]Mast cell tumour NOS
92703	B560400	Secondary and unspec malig neop deep parotid lymph nodes
93136	L241000	Tumour of uterine body affecting obstetric care
93218	B03z.00	Malignant neoplasm of gum NOS
93478	B138.00	Malignant neoplasm, overlapping lesion of colon
93537	B517200	Malignant neoplasm of midbrain
93762	B42..00	Malignant neoplasm of placenta
93778	B1z1z00	Malignant neoplasm of spleen NOS
93842	B062300	Malignant neoplasm of palatopharyngeal arch
94220	B540100	Malignant neoplasm of adrenal medulla
94251	B00z100	Malignant neoplasm of lip, unspecified, lipstick area
94278	B110111	Malignant neoplasm of gastro-oesophageal junction
94355	B55y200	Malignant neoplasm of flank NOS
94390	B070.00	Malignant neoplasm of roof of nasopharynx
94415	B623100	Malignant histiocytosis of lymph nodes head, face and neck
94427	B305C00	Malignant neoplasm of fifth metacarpal bone
94441	B003300	Malignant neoplasm of lower lip, oral aspect
94776	B1z2.00	Malignant neoplasm, overlapping lesion of digestive system
94975	B241300	Malignant neoplasm of pericardium
95016	B0z1.00	Malignant neoplasm of Waldeyer's ring
95182	B308100	Malignant neoplasm of talus
95323	B35z000	Malignant neoplasm of ectopic site of male breast
95334	G210000	Malignant hypertensive heart disease without CCF
95373	BBCC100	[M]Leydig cell tumour, malignant
95421	B45y.00	Malignant neoplasm of other specified female genital organ
95429	B071.00	Malignant neoplasm of posterior wall of nasopharynx
95458	B300300	Malignant neoplasm of nasal bone
95480	B001100	Malignant neoplasm of lower lip, lipstick area
95505	B41y000	Malignant neoplasm of cervical stump
95603	BBZ0.00	[M]Odontogenic tumour, benign

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
95609	BB5B300	[M]Insulinoma, malignant
95629	B325500	Malignant melanoma of perineum
95644	B241.00	Malignant neoplasm of heart
95671	Byu5700	[X]Malignant neoplasm of peritoneum, unspecified
95772	B051000	Malignant neoplasm of upper buccal sulcus
95783	B17yz00	Malignant neoplasm of specified site of pancreas NOS
95818	BBD1.00	[M]Paraganglioma, malignant
96003	B055000	Malignant neoplasm of junction of hard and soft palate
96226	ByuC100	[X]Malignant neoplasm/overlap lesion/other+ill-defined sites
96231	BBGJ.00	[M]Fibroxanthoma, malignant
96429	B470z00	Malignant neoplasm of undescended testis NOS
96445	B300B00	Malignant neoplasm of turbinate
96585	B32y000	Overlapping malignant melanoma of skin
96635	B17y000	Malignant neoplasm of ectopic pancreatic tissue
96713	BBUz.00	[M]Lymphatic vessel tumour NOS
96782	B003z00	Malignant neoplasm of lower lip, inner aspect NOS
96783	B005.00	Malignant neoplasm of commissure of lip
96802	B11y100	Malignant neoplasm of posterior wall of stomach NEC
96869	B071z00	Malignant neoplasm of posterior wall of nasopharynx NOS
97091	ByuC500	[X]2ndry malignant neoplasm/bladder+oth+unsp urinary organs
97332	B213z00	Malignant neoplasm of laryngeal cartilage NOS
97530	B051100	Malignant neoplasm of lower buccal sulcus
97547	B551200	Malignant neoplasm of intrathoracic site NOS
97593	BBZG.00	[M]Ameloblastoma, malignant
97775	C13y300	Diencephalic syndrome secondary to tumour
97832	B58y211	Secondary cancer of the cervix
97593	BBZG.00	[M]Ameloblastoma, malignant
97852	BBk7.00	[M]Malignant lymphoma, centroblastic type, follicular
97875	B175.00	Malignant neoplasm, overlapping lesion of pancreas
97996	B44y.00	Malignant neoplasm of other site of uterine adnexa
98019	BBZD.00	[M]Adenomatoid odontogenic tumour
98104	B23y.00	Malignant neoplasm of other specified pleura
98322	BBT7100	[M]Haemangioendothelioma, malignant
98500	B002200	Malignant neoplasm of upper lip, mucosa
98537	B201100	Malignant neoplasm of tympanic cavity
98559	BBW8.00	[M]Chondroblastoma, malignant
98740	B000z00	Malignant neoplasm of upper lip, vermilion border NOS
98911	B200100	Malignant neoplasm of nasal conchae
98961	BBk2.00	[M]Malignant lymphoma, centroblastic-centrocytic, follicular
99001	B002100	Malignant neoplasm of upper lip, frenulum
99096	Byu2300	[X]Malignant neopl/overlapping les/resp+intrathoracic organs
99185	B062100	Malignant neoplasm of glossopalatine fold
99219	BBCCz11	[M]Interstitial cell tumour NOS
99257	B324z00	Malignant melanoma of scalp and neck NOS
99296	BB5R400	[M]Carcinoid tumour, nonargentaffin, NOS
99386	B073200	Malignant neoplasm posterior margin nasal septum and choanae

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
99493	B002.00	Malignant neoplasm of upper lip, inner aspect
99511	B574200	Secondary malignant neoplasm of ileum
99572	B312500	Malignant neoplasm of connective and soft tissue of toe
99621	B520.00	Malignant neoplasm of cranial nerves
99702	BBn3.00	[M]Plasma cell tumour, malignant
99797	BBX3.00	[M]Malignant giant cell tumour of soft parts
99896	B12y.00	Malignant neoplasm of other specified site small intestine
99913	B510300	Malignant neoplasm of globus pallidus
99949	BBa0.11	[M]Rathke's pouch tumour
100002	B062z00	Malignant neoplasm of tonsillar fossa NOS
100035	1J0L.00	Suspected malignant mesothelioma
100112	BB03.13	[M]Tumour embolism
100144	B004300	Malignant neoplasm of lip, oral aspect
100210	B905400	Gastrointestinal stromal tumour
100267	BBZG.11	[M]Adamantinoma, malignant
100296	B582100	Secondary malignant neoplasm of skin of face
100561	L241200	Tumour of uterine body - baby delivered + p/n complication
100584	B110000	Malignant neoplasm of cardiac orifice of stomach
100590	BB03.12	[M]Tumour embolus
100625	BB5R500	[M]Carcinoid tumour, nonargentaffin, malignant
100721	B002z00	Malignant neoplasm of upper lip, inner aspect NOS
100733	B51yz00	Malignant neoplasm of other part of brain NOS
100906	B00z000	Malignant neoplasm of lip, unspecified, external
100918	B073z00	Malignant neoplasm of anterior wall of nasopharynx NOS
101086	B520z00	Malignant neoplasm of cranial nerves NOS
101429	BBj0.11	[M]Lymphogranuloma, malignant
101568	BBZz.00	[M]Odontogenic tumour NOS
101608	B4A1100	Malignant neoplasm of ureteropelvic junction
101700	B139.00	Hereditary nonpolyposis colon cancer
101707	B001z00	Malignant neoplasm of lower lip, vermilion border NOS
101753	B03y.00	Malignant neoplasm of other sites of gum
101778	B442.00	Malignant neoplasm of broad ligament
101805	B507000	Malignant neoplasm of lacrimal sac
101836	A788600	Human immunodeficiency virus with secondary cancers
101885	B241400	Mesothelioma of pericardium
101988	B060100	Malignant neoplasm of palatine tonsil
102142	B013000	Malignant neoplasm of anterior 2/3 of tongue ventral surface
102145	B322100	Malignant melanoma of external auditory meatus
102151	B060200	Malignant neoplasm of overlapping lesion of tonsil
102205	B072z00	Malignant neoplasm of lateral wall of nasopharynx NOS
102688	ByuD400	[X]Other malignant immunoproliferative diseases
102949	B312000	Malignant neoplasm of connective and soft tissue of hip
103034	BB5j500	[M]Endometrioid adenofibroma, malignant
103046	G210z00	Malignant hypertensive heart disease NOS
103354	B308z00	Malignant neoplasm of short bones of leg NOS
103796	B051.00	Malignant neoplasm of vestibule of mouth

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
103946	B220100	Malignant neoplasm of mucosa of trachea
348	B34..11	Cancer female breast
21715	Byu5011	[X]Mesothelioma of lung
24374	B0...11	Carcinoma of lip, oral cavity and pharynx
30526	Byu5100	[X]Mesothelioma, unspecified
50290	B6z0.00	Kaposi's sarcoma of lymph nodes
60053	Byu..00	[X]Additional neoplasm classification terms
67034	Byu5000	[X]Mesothelioma of other sites
91896	Byu5800	[X]Mal neoplasm/connective+soft tissue of trunk,unspecified
93665	Byu5300	[X]Kaposi's sarcoma, unspecified
98361	Byu5B00	[X]Kaposi's sarcoma of other sites
101668	Byu5400	[X]Malignant neoplasm/peripheral nerves of trunk,unspecified
105072	Byu5500	[X]Mal neoplasm/overlap les/periph nerv+autonomic nerv systm
37549	B05z000	Kaposi's sarcoma of palate
104128	B31z000	Kaposi's sarcoma of soft tissue
65466	B592X00	Kaposi's sarcoma of multiple organs
49525	B59zX00	Kaposi's sarcoma, unspecified
9984	B00..11	Carcinoma of lip
99493	B002.00	Malignant neoplasm of upper lip, inner aspect
47205	B017.00	Malignant overlapping lesion of tongue
37516	B054.00	Malignant neoplasm of uvula
33388	B071000	Malignant neoplasm of adenoid
46114	B0z..00	Malig neop other/ill-defined sites lip, oral cavity, pharynx
3357	B1...11	Carcinoma of digestive organs and peritoneum
98142	B107.00	Siewert type I adenocarcinoma
10368	B11..11	Gastric neoplasm
97499	B118.00	Siewert type II adenocarcinoma
96094	B119.00	Siewert type III adenocarcinoma
22163	B134.11	Carcinoma of caecum
93478	B138.00	Malignant neoplasm, overlapping lesion of colon
9118	B13z.11	Colonic cancer
7219	B141.11	Carcinoma of rectum
5901	B141.12	Rectal carcinoma
9491	B142.11	Anal carcinoma
55659	B14y.00	Malig neop other site rectum, rectosigmoid junction and anus
16126	B150000	Primary carcinoma of liver
22187	B150300	Hepatocellular carcinoma
36147	B153.00	Secondary malignant neoplasm of liver
31393	B160.11	Carcinoma gallbladder
36495	B161211	Carcinoma common bile duct
105613	B161300	Malignant neoplasm of sphincter of Oddi
35039	B163.00	Malignant neoplasm, overlapping lesion of biliary tract
97875	B175.00	Malignant neoplasm, overlapping lesion of pancreas
101907	B182.00	Overlapping malign lesion of retroperitoneum and peritoneum
50898	B18y300	Malignant neoplasm of omentum
11009	B1z..00	Malig neop oth/ill-defined sites digestive tract/peritoneum

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
94776	B1z2.00	Malignant neoplasm, overlapping lesion of digestive system
34075	B2...00	Malig neop of respiratory tract and intrathoracic organs
45307	B2...11	Carcinoma of respiratory tract and intrathoracic organs
26652	B20..00	Malig neop nasal cavities, middle ear and accessory sinuses
62182	B200300	Malignant neoplasm of vestibule of nose
24456	B201.00	Malig neop auditory tube, middle ear and mastoid air cells
73537	B201z00	Malig neop auditory tube, middle ear, mastoid air cells NOS
96971	B20y.00	Malig neop other site nasal cavity, middle ear and sinuses
33444	B221100	Malignant neoplasm of hilus of lung
42566	B224z00	Malignant neoplasm of lower lobe, bronchus or lung NOS
106194	B231.00	Malignant neoplasm of visceral pleura
92720	B243.00	Malignant neoplasm of posterior mediastinum
100232	B24y.00	Malig neop of other site of heart, thymus and mediastinum
39531	B25..00	Malig neo, overlapping lesion of heart, mediastinum & pleura
44356	B2z..00	Malig neop other/ill-defined sites resp/intrathoracic organs
65793	B2z0.00	Malig neop of upper respiratory tract, part unspecified
18608	B3...00	Malig neop of bone, connective tissue, skin and breast
9902	B3...11	Carcinoma of bone, connective tissue, skin and breast
44452	B300C00	Malignant neoplasm of vomer
105797	B304100	Malignant neoplasm of acromion
65880	B304z00	Malig neop of scapula and long bones of upper arm NOS
106069	B305.11	Malignant neoplasm of carpal bones
73556	B305z00	Malignant neoplasm of hand bones NOS
105475	B308.00	Malignant neoplasm of short bones of leg
43475	B310.00	Malig neop of connective and soft tissue head, face and neck
73718	B310z00	Malig neop connective and soft tissue head, face, neck NOS
53989	B311.00	Malig neop connective and soft tissue upper limb/shoulder
104913	B311z00	Malig neop connective soft tissue upper limb/shoulder NOS
66088	B312.00	Malig neop of connective and soft tissue of hip and leg
44805	B312100	Malig neop of connective and soft tissue thigh and upper leg
30542	B312300	Malig neop of connective and soft tissue of lower leg
90546	B312z00	Malig neop connective and soft tissue hip and leg NOS
104139	B313300	Malig neoplasm of connective and soft tissues of thor spine
98408	B313z00	Malig neop of connective and soft tissue of thorax NOS
66488	B314000	Malig neop of connective and soft tissue of abdominal wall
94272	B314100	Malig neoplasm of connective and soft tissues of lumb spine
60247	B314z00	Malig neop of connective and soft tissue of abdomen NOS
67324	B315100	Malig neop of connective and soft tissue of inguinal region
58836	B315z00	Malig neop of connective and soft tissue of pelvis NOS
57471	B316.00	Malig neop of connective and soft tissue trunk unspecified
65233	B31y.00	Malig neop connective and soft tissue other specified site
34259	B325300	Malignant melanoma of groin
54685	B326100	Malignant melanoma of upper arm
62475	B326300	Malignant melanoma of hand
64686	B340100	Malignant neoplasm of areola of female breast
95057	B34y000	Malignant neoplasm of ectopic site of female breast

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
105488	B36..00	Local recurrence of malignant tumour of breast
19389	B3y..00	Malig neop of bone, connective tissue, skin and breast OS
41011	B3z..00	Malig neop of bone, connective tissue, skin and breast NOS
16874	B4...11	Carcinoma of genitourinary organ
3230	B41..11	Cervical carcinoma (uterus)
28003	B420.00	Choriocarcinoma
33617	B43z.00	Malignant neoplasm of body of uterus NOS
4555	B45..00	Malig neop of other and unspecified female genital organs
4554	B454.00	Malignant neoplasm of vulva unspecified
28241	B496.00	Malignant neoplasm of ureteric orifice
13559	B4A..00	Malig neop of kidney and other unspecified urinary organs
8693	B5...11	Carcinoma of other and unspecified sites
98813	B500.00	Malig neop eyeball excl conjunctiva, cornea, retina, choroid
65241	B51y200	Malignant neoplasm, overlapping lesion of brain
65458	B52..00	Malig neop of other and unspecified parts of nervous system
24235	B524.00	Malig neopl peripheral nerves and autonomic nervous system
50777	B524600	Malignant neoplasm,overlap lesion periph nerve & auton ns
53504	B52W.00	Malig neopl, overlap lesion brain & other part of CNS
30511	B54..00	Malig neop of other endocrine glands and related structures
59823	B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct
59718	B542z00	Malig neop pituitary gland or craniopharyngeal duct NOS
103995	B545z00	Malignant neoplasm of aortic body or paraganglia NOS
64195	B54z.00	Malig neop of endocrine gland or related structure NOS
49214	B560.00	Secondary and unspec malig neop lymph nodes head/face/neck
64918	B560000	Secondary and unspec malig neop of superficial parotid LN
33395	B560200	Secondary and unspec malig neop superficial cervical LN
39433	B560500	Secondary and unspec malig neop submandibular lymph nodes
28059	B560600	Secondary and unspec malig neop of facial lymph nodes
38343	B560700	Secondary and unspec malig neop submental lymph nodes
44627	B560800	Secondary and unspec malig neop anterior cervical LN
68611	B560900	Secondary and unspec malig neop deep cervical LN
67129	B560z00	Secondary unspec malig neop lymph nodes head/face/neck NOS
64116	B561.00	Secondary and unspec malig neop intrathoracic lymph nodes
37919	B561000	Secondary and unspec malig neop internal mammary lymph nodes
105953	B561100	Secondary and unspec malig neop intercostal lymph nodes
95378	B561200	Secondary and unspec malig neop diaphragmatic lymph nodes
25366	B561300	Secondary and unspec malig neop ant mediastinal lymph nodes
55463	B561400	Secondary and unspec malig neop post mediastinal lymph nodes
58692	B561500	Secondary and unspec malig neop paratracheal lymph nodes
67797	B561600	Secondary and unspec malig neop superfic tracheobronchial LN
69392	B561700	Secondary and unspec malig neop inferior tracheobronchial LN
62124	B561800	Secondary and unspec malig neop bronchopulmonary lymph nodes
52190	B561900	Secondary and unspec malig neop pulmonary lymph nodes
93716	B561z00	Secondary and unspec malig neop intrathoracic LN NOS
52736	B562.00	Secondary and unspec malig neop intra-abdominal lymph nodes
41691	B562000	Secondary and unspec malig neop coeliac lymph nodes

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
72713	B562100	Secondary and unspec malig neop superficial mesenteric LN
61677	B562200	Secondary and unspec malig neop inferior mesenteric LN
18658	B562300	Secondary and unspec malig neop common iliac lymph nodes
69132	B562400	Secondary and unspec malig neop external iliac lymph nodes
44931	B562z00	Secondary and unspec malig neop intra-abdominal LN NOS
50199	B563.00	Secondary and unspec malig neop axilla and upper limb LN
37540	B563000	Secondary and unspec malig neop axillary lymph nodes
98626	B563100	Secondary and unspec malig neop supratrochlear lymph nodes
50904	B563200	Secondary and unspec malig neop infraclavicular lymph nodes
46409	B563300	Secondary and unspec malig neop pectoral lymph nodes
73538	B563z00	Secondary and unspec malig neop axilla and upper limb LN NOS
54278	B564000	Secondary and unspec malig neop superficial inguinal LN
61289	B564100	Secondary and unspec malig neop deep inguinal lymph nodes
70747	B564z00	Secondary and unspec malig neop of inguinal and leg LN NOS
6701	B565.00	Secondary and unspec malig neop intrapelvic lymph nodes
84368	B565000	Secondary and unspec malig neop internal iliac lymph nodes
101662	B565200	Secondary and unspec malig neop circumflex iliac LN
47366	B565300	Secondary and unspec malig neop sacral lymph nodes
72803	B565z00	Secondary and unspec malig neop intrapelvic LN NOS
20159	B56y.00	Secondary and unspec malig neop lymph nodes multiple sites
15507	B56z.00	Secondary and unspec malig neop lymph nodes NOS
35053	B57..00	Secondary malig neop of respiratory and digestive systems
6471	B57..11	Metastases of respiratory and/or digestive systems
24301	B57..12	Secondary carcinoma of respiratory and/or digestive systems
4137	B570.00	Secondary malignant neoplasm of lung
4137	B570.00	Secondary malignant neoplasm of lung
70026	B574z00	Secondary malig neop of small intestine or duodenum NOS
36200	B575z00	Secondary malig neop of large intestine or rectum NOS
97672	B576z00	Secondary malig neop of retroperitoneum or peritoneum NOS
4403	B577.11	Liver metastases
66083	B57z.00	Secondary malig neop of respiratory or digestive system NOS
27651	B58..11	Secondary carcinoma of other specified sites
41144	B582300	Secondary malignant neoplasm of skin of trunk
55096	B582z00	Secondary malignant neoplasm of skin NOS
55096	B582z00	Secondary malignant neoplasm of skin NOS
5198	B583000	Secondary malignant neoplasm of brain
5199	B583200	Cerebral metastasis
18676	B585000	Pathological fracture due to metastatic bone disease
36401	B587.00	Secondary malignant neoplasm of adrenal gland
73616	B58y200	Secondary malignant neoplasm of cervix uteri
60335	B58y400	Secondary malignant neoplasm of vulva
21590	B58y500	Secondary malignant neoplasm of prostate
104480	B58y800	Secondary malignant neoplasm of epididymis and vas deferens
13569	B590.00	Disseminated malignancy NOS
6170	B590.11	Carcinomatosis
105025	ByuDA00	[X]Oth spcf mal neoplsm/lymphoid,haematopoietic+rltd tissue

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
72500	ByuDB00	[X]Mal neoplasm/lymphoid,haematopoietic+related tissu,unspcf
9102	BBY..00	[M]Miscellaneous bone tumours
43490	Byu1100	[X]Other specified carcinomas of liver
40595	Byu2000	[X]Malignant neoplasm of bronchus or lung, unspecified
47633	ByuA300	[X]Malig neopl, overlap lesion brain & other part of CNS
33508	BB0z.00	[M]Unspecified tumour cell NOS
49629	BB5C100	[M]Gastrinoma, malignant
3923	BB5R.00	[M]Carcinoid tumours
38444	BB5R000	[M]Carcinoid tumour NOS
24924	BBD..00	[M]Paragangliomas and glomus tumours
45953	BBD4.00	[M]Glomus jugulare tumour
44318	B62xX00	Oth and unspecif peripheral & cutaneous T-cell lymphomas
64427	B62z100	Unspec malig neop lymphoid/histiocytic lymph node head/neck
93384	B62z200	Unspec malig neop lymphoid/histiocytic of intrathoracic node
103353	B62z300	Unspec malig neop lymphoid/histiocytic intra-abdominal nodes
71609	B62z500	Unspec malig neop lymphoid/histiocytic nodes inguinal/leg
101465	B62z800	Unspec malig neop lymphoid/histiocytic of multiple sites
95792	B62zz00	Lymphoid and histiocytic malignancy NOS
70716	B62zz11	Immunoproliferative neoplasm
37182	B63..00	Multiple myeloma and immunoproliferative neoplasms
104324	B595.00	Malignant tumour of unknown origin
105388	B498.00	Local recurrence of malignant tumour of urinary bladder
43450	B63z.00	Immunoproliferative neoplasm or myeloma NOS
64567	B63y.00	Other immunoproliferative neoplasms
103900	B626000	Mast cell malignancy of unspecified site
100615	B626500	Mast cell malignancy of lymph nodes inguinal region and leg
31324	B626800	Mast cell malignancy of lymph nodes of multiple sites
68410	B150200	Primary angiosarcoma of liver
17874	B181.00	Mesothelioma of peritoneum
7484	B226.00	Mesothelioma
9600	B232.00	Mesothelioma of pleura
12539	B3...12	Sarcoma of bone and connective tissue
19437	B30z000	Osteosarcoma
7740	B470200	Seminoma of undescended testis
36325	B470300	Teratoma of undescended testis
21786	B471000	Seminoma of descended testis
9476	B471100	Teratoma of descended testis
2961	B47z.11	Seminoma of testis
15989	B47z.12	Teratoma of testis
7978	B4A0000	Hypernephroma
18231	B540.11	Phaeochromocytoma
7830	B56..11	Lymph node metastases
41369	B60..00	Lymphosarcoma and reticulosarcoma
99887	B60y.00	Other specified reticulosarcoma or lymphosarcoma
99951	B60z.00	Reticulosarcoma or lymphosarcoma NOS
95715	B627900	Mucosa-associated lymphoma

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
95545	B627911	Maltoma
17182	B627C11	Follicular lymphoma NOS
104152	B628.00	Follicular lymphoma
105889	B628000	Follicular lymphoma grade 1
105095	B628100	Follicular lymphoma grade 2
105020	B628300	Follicular lymphoma grade 3a
106063	B628700	Other types of follicular lymphoma
4944	B630.00	Multiple myeloma
43552	B630.11	Kahler's disease
15211	B630.12	Myelomatosis
19028	B630100	Solitary myeloma
21329	B630200	Plasmacytoma NOS
104418	B630400	Solitary plasmacytoma
70724	B653.00	Myeloid sarcoma
39629	B653100	Granulocytic sarcoma
43415	ByuD000	[X]Other Hodgkin's disease
67518	ByuD100	[X]Other types of follicular non-Hodgkin's lymphoma
98596	ByuD200	[X]Other types of diffuse non-Hodgkin's lymphoma
64336	ByuD300	[X]Other specified types of non-Hodgkin's lymphoma
64515	ByuDC00	[X]Diffuse non-Hodgkin's lymphoma, unspecified
63375	ByuDE00	[X]Unspecified B-cell non-Hodgkin's lymphoma
8649	ByuDF00	[X]Non-Hodgkin's lymphoma, unspecified type
7940	ByuDF11	[X]Non-Hodgkin's lymphoma NOS
3604	B627.00	Non - Hodgkin's lymphoma
104391	B627.11	Non-Hodgkin lymphoma
28639	B627000	Follicular non-Hodgkin's small cleaved cell lymphoma
49262	B627200	Follicular non-Hodgkin's large cell lymphoma
50668	B627300	Diffuse non-Hodgkin's small cell (diffuse) lymphoma
50695	B627500	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma
53551	B627600	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma
17460	B627700	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
65180	B627800	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
101114	B627A00	Diffuse non-Hodgkin's large cell lymphoma
31576	B627B00	Other types of follicular non-Hodgkin's lymphoma
21549	B627C00	Follicular non-Hodgkin's lymphoma
70509	B627D00	Diffuse non-Hodgkin's centroblastic lymphoma
31794	B627W00	Unspecified B-cell non-Hodgkin's lymphoma
39798	B627X00	Diffuse non-Hodgkin's lymphoma, unspecified
2462	B61..00	Hodgkin's disease
104291	B61..11	Hodgkin lymphoma
29178	B614.00	Hodgkin's disease, nodular sclerosis
57225	B614000	Hodgkin's disease, nodular sclerosis of unspecified site
55303	B614100	Hodgkin's nodular sclerosis of head, face and neck
67506	B614200	Hodgkin's nodular sclerosis of intrathoracic lymph nodes
61149	B614300	Hodgkin's nodular sclerosis of intra-abdominal lymph nodes
65483	B614400	Hodgkin's nodular sclerosis of lymph nodes of axilla and arm

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
105472	B614700	Hodgkin's disease, nodular sclerosis of spleen
19140	B614800	Hodgkin's nodular sclerosis of lymph nodes of multiple sites
63054	B614z00	Hodgkin's disease, nodular sclerosis NOS
49605	B615.00	Hodgkin's disease, mixed cellularity
97863	B615000	Hodgkin's disease, mixed cellularity of unspecified site
94407	B615100	Hodgkin's mixed cellularity of lymph nodes head, face, neck
58684	B615200	Hodgkin's mixed cellularity of intrathoracic lymph nodes
94005	B615z00	Hodgkin's disease, mixed cellularity NOS
67703	B616.00	Hodgkin's disease, lymphocytic depletion
95049	B616000	Hodgkin's lymphocytic depletion of unspecified site
63625	B616400	Hodgkin's lymphocytic depletion lymph nodes axilla and arm
101715	B616700	Hodgkin's disease, lymphocytic depletion of spleen
101530	B616z00	Hodgkin's disease, lymphocytic depletion NOS
104895	B617.00	Nodular lymphocyte predominant Hodgkin lymphoma
105841	B618.00	Nodular sclerosis classical Hodgkin lymphoma
104484	B61C.00	Other classical Hodgkin lymphoma
53397	B61z.00	Hodgkin's disease NOS
61662	B61z000	Hodgkin's disease NOS, unspecified site
59778	B61z100	Hodgkin's disease NOS of lymph nodes of head, face and neck
59755	B61z200	Hodgkin's disease NOS of intrathoracic lymph nodes
91900	B61z400	Hodgkin's disease NOS of lymph nodes of axilla and arm
99012	B61z500	Hodgkin's disease NOS of lymph nodes inguinal region and leg
94279	B61z700	Hodgkin's disease NOS of spleen
97746	B61z800	Hodgkin's disease NOS of lymph nodes of multiple sites
42461	B61zz00	Hodgkin's disease NOS
64036	B612.00	Hodgkin's sarcoma
68039	B612400	Hodgkin's sarcoma of lymph nodes of axilla and upper limb
5179	B620.00	Nodular lymphoma (Brill - Symmers disease)
66327	B620000	Nodular lymphoma of unspecified site
45264	B620100	Nodular lymphoma of lymph nodes of head, face and neck
105203	B620200	Nodular lymphoma of intrathoracic lymph nodes
92068	B620300	Nodular lymphoma of intra-abdominal lymph nodes
94995	B620500	Nodular lymphoma of lymph nodes of inguinal region and leg
58082	B620800	Nodular lymphoma of lymph nodes of multiple sites
65701	B620z00	Nodular lymphoma NOS
71625	B601000	Lymphosarcoma of unspecified site
71238	B601100	Lymphosarcoma of lymph nodes of head, face and neck
62380	B601200	Lymphosarcoma of intrathoracic lymph nodes
64670	B601300	Lymphosarcoma of intra-abdominal lymph nodes
100352	B601500	Lymphosarcoma of lymph nodes of inguinal region and leg
103245	B601700	Lymphosarcoma of spleen
104790	B601800	Lymphosarcoma of lymph nodes of multiple sites
63723	B601z00	Lymphosarcoma NOS
59115	B602100	Burkitt's lymphoma of lymph nodes of head, face and neck
100006	B602200	Burkitt's lymphoma of intrathoracic lymph nodes
97577	B602300	Burkitt's lymphoma of intra-abdominal lymph nodes

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
92380	B602500	Burkitt's lymphoma of lymph nodes of inguinal region and leg
71304	B602z00	Burkitt's lymphoma NOS
21402	B602.00	Burkitt's lymphoma
1481	B600.00	Reticulosarcoma
60242	B600000	Reticulosarcoma of unspecified site
71031	B600100	Reticulosarcoma of lymph nodes of head, face and neck
70374	B600300	Reticulosarcoma of intra-abdominal lymph nodes
95058	B600700	Reticulosarcoma of spleen
99240	B600z00	Reticulosarcoma NOS
27330	B624.00	Leukaemic reticuloendotheliosis
5137	B624.11	Leukaemic reticuloendotheliosis
87335	B624.12	Hairy cell leukaemia
65122	B624000	Leukaemic reticuloendotheliosis of unspecified sites
65123	B624300	Leukaemic reticuloend of intra-abdominal lymph nodes
73777	B624z00	Leukaemic reticuloendotheliosis NOS
39187	B631.00	Plasma cell leukaemia
19372	B64..00	Lymphoid leukaemia
4222	B64..11	Lymphatic leukaemia
4251	B640.00	Acute lymphoid leukaemia
104325	B640000	B-cell acute lymphoblastic leukaemia
8625	B641.00	Chronic lymphoid leukaemia
27790	B641.11	Chronic lymphatic leukaemia
104328	B641000	B-cell chronic lymphocytic leukaemia
72774	B642.00	Subacute lymphoid leukaemia
37461	B64y200	Adult T-cell leukaemia
104939	B64y500	Adult T-cell lymphoma/leukaemia (HTLV-1-associated)
38331	B64yz00	Other lymphoid leukaemia NOS
38914	B64z.00	Lymphoid leukaemia NOS
7176	B65..00	Myeloid leukaemia
4413	B650.00	Acute myeloid leukaemia
10726	B651.00	Chronic myeloid leukaemia
31701	B651.11	Chronic granulocytic leukaemia
100786	B651000	Chronic eosinophilic leukaemia
105957	B651100	Chronic myeloid leukaemia, BCR/ABL positive
102783	B651200	Chronic neutrophilic leukaemia
27520	B651z00	Chronic myeloid leukaemia NOS
49725	B64y.00	Other lymphoid leukaemia
67029	ByuD500	[X]Other lymphoid leukaemia
61693	ByuD600	[X]Other myeloid leukaemia
89762	ByuD700	[X]Other monocytic leukaemia
89329	ByuD800	[X]Other specified leukaemias
65165	ByuD900	[X]Other leukaemia of unspecified cell type
63475	B652.00	Subacute myeloid leukaemia
104788	B654.00	Acute myeloblastic leukaemia
27664	B65y100	Acute promyelocytic leukaemia
66089	B65yz00	Other myeloid leukaemia NOS

(Continued) Appendix 8 Read code list of cancer conditions

Medcode	Read codes	Cancer terms
35875	B66..00	Monocytic leukaemia
67700	B66..12	Monoblastic leukaemia
19974	B660.00	Acute monocytic leukaemia
27458	B661.00	Chronic monocytic leukaemia
101606	B662.00	Subacute monocytic leukaemia
99015	B66y.00	Other monocytic leukaemia
103645	B66yz00	Other monocytic leukaemia NOS
93342	B66z.00	Monocytic leukaemia NOS
37272	B67..00	Other specified leukaemia
42539	B670.00	Acute erythraemia and erythroleukaemia
57671	B672.00	Megakaryocytic leukaemia
65777	B672.11	Thrombocytic leukaemia
65721	B673.00	Mast cell leukaemia
72197	B67y000	Lymphosarcoma cell leukaemia
94174	B67y.00	Other and unspecified leukaemia
99413	B67yz00	Other and unspecified leukaemia NOS
30632	B67z.00	Other specified leukaemia NOS
25191	B68..00	Leukaemia of unspecified cell type
4072	B680.00	Acute leukaemia NOS
16416	B681.00	Chronic leukaemia NOS
54793	B682.00	Subacute leukaemia NOS
34692	B68y.00	Other leukaemia of unspecified cell type
4250	B68z.00	Leukaemia NOS
20440	B69..00	Myelomonocytic leukaemia
61500	B690.00	Acute myelomonocytic leukaemia
22050	B691.00	Chronic myelomonocytic leukaemia
104475	B692.00	Subacute myelomonocytic leukaemia

Appendix 9 Annual CPRD registrants, by age and sex

Year	Registrants	N (%)		N (%)	
	All	Male	Female	<60 years	≥60 years
2000	3,483,675	1,667,431 (47.86)	1,816,101 (52.13)	2,523,160 (72.43)	960,515 (27.57)
2001	3,857,091	1,847,128 (47.89)	2,009,762 (52.11)	2,826,685 (73.29)	1,030,406 (26.71)
2002	4,176,404	1,998,409 (47.85)	2,177,728 (52.14)	3,080,887 (73.77)	1,095,517 (26.23)
2003	4,348,348	2,080,416 (47.84)	2,267,578 (52.15)	3,235,846 (74.42)	1,112,502 (25.58)
2004	4,505,355	2,155,064 (47.83)	2,349,943 (52.16)	3,382,187 (75.07)	1,123,168 (24.93)
2005	4,599,323	2,197,171 (47.77)	2,401,780 (52.22)	3,482,544 (75.72)	1,116,779 (24.28)
2006	4,726,748	2,255,289 (47.71)	2,471,083 (52.28)	3,602,159 (76.21)	1,124,589 (23.79)
2007	4,828,875	2,299,131 (47.61)	2,529,297 (52.38)	3,691,171 (76.44)	1,137,704 (23.56)
2008	4,840,725	2,301,766 (47.55)	2,538,476 (52.44)	3,722,449 (76.90)	1,118,276 (23.10)
2009	4,833,078	2,293,275 (47.45)	2.539,272 (52.54)	3,735,959 (77.30)	1,097,119 (22.70)
2010	4,884,492	2,314,721 (47.39)	2,569,220 (52.60)	3,795,692 (77.71)	1,088,800 (22.29)

Appendix 10 Parameters specified in joinpoint regression program

Parameters	Value
Model	In(y) = bx
Dependent variable	Number of strong opioid prescriptions, incidence and prevalence of strong opioid users in person-years
Independent variable	Year
Heteroscedastic errors option	Constant variance (homoscedasticity)
Number of joinpoints	Min=0 Max=1
Method	Grid search method
Maximum number of observations from a joinpoint to either end of the data	2
Minimum number of observations between two joinpoints	1
Model Selection Method	Permutation test based on Monte Carlo
Significance level	0.05
Number of permutations	4499

Appendix 11 List of pain conditions traced in CPRD browser

Conditions
Osteoarthritis
Fibromyalgia
Back pain
Shoulder pain
Neck pain
Sciatica
Thoracic pain
Neuropathy
Headache
Migraine
Abdominal pain
Unspecified arthritis
Rheumatoid arthritis
Ankylosing spondylitis
Lupus
Psoriatic arthritis
Colitis
Crohn's disease arthritis
Gout
Pancreatitis
Spinal pain
Cervical spondylitis
Post herpetic neuralgia
Phantom limb pain
Complex regional pain syndrome
Trigeminal neuralgia
Facial pain
Temporomandibular joint disorder
Gallstones
Cervical pain
Menstrual pain
Pelvic pain
Postoperative pain

Appendix 12 Read codes of QOF long-term morbidities

Read code	Condition
G573.	Atrial fibrillation
G2... G20.. G24.. G2z.. Gyu2. Gyu20 246..	Hypertension
1Z12. 1Z13. 1Z14. 1Z15. 1Z16. 1Z1B. 1Z1L. K053. K054. K055	Coronary kidney disease (CKD)
Eu02. E00.. Eu01. E02y1 E012. Eu00. E041. Eu041 F110. F112. F116.	Dementia
F25.. F258. F25A. F25y4 F25G. F25h. F1321 SC200	Epilepsy
G58.. G1yz1 662f. 662i 662G 9hH Q48 585f G5yy9 G5yyD 5853. 58531 585f. 585g. 5C20. 33BD. 8HQ7. R1320 R1322 5531. 5533. 5538. 79380 79382 8H4R. 8HVJ. 8H44. 8H7o0 7P0H6 8A544 8HTL0 8HTL. 79352 7P0H. 7P0H0 7P0H1 7P0H4	Heart failure
E3... Eu7.. Eu814 Eu815 Eu816 Eu817 Eu81z Eu818 918e	Learning disability
E10.. E110. E111. E1124 E1134 E114. E117z E11y. E13.. E2122, Eu2.. Eu30. Eu31. Eu323, Eu328, Eu333 Eu32A Eu329	Mental health illness
22K5. 22K7. 22A5 222A	Obesity
N331N N331M N330. N3312 N3313 N3316 N3318 N331B N331H N331M NyuB0 NyuB1 NyuB8 N3314 N3315 N3746 NyuB2 58EG. 58EM. 58EV. 58EE. 58EK. 58ES.	Osteoporosis
N040. N041. N042. N047. N04X. N04y0 N04y2 Nyu11 Nyu12 Nyu1G Nyu10 G5yA. G5y8.	Rheumatoid arthritis
C03.. C04..	Hypothyroidism
H33.. H3120 173A.	Asthma
H3… H31.. H32.. H36.. H3z.. H5832	COPD
C10.. C109J C109K C10C. C10D. C10E. C10F. C10G. C10H. C10M. C10N. PKyP.	Diabetes
G3… G309. G30B. G330z G33z. G3401 G342. G35X. G38.. G3z.. Gyu3. G30.. G35.. G38.. Gyu34 Gyu36 246..	Coronary heart disease
G61.. G63y0 G63y1 G64.. G66.. G6760 G6W.. G6X.. Gyu62 Gyu66 Gyu6F Gyu6G G619. G65.. G654. G656. G65zz ZV12D Fyu55 G619. G665.	Stroke

Note: QOF business rule 27 was used [246].

Appendix 13 Read code list of psychiatric conditions

Depression		
Medcode	**Read code**	**Term**
655	E135.00	Agitated depression
543	E111.14	Endogenous depression
5987	E113700	Recurrent depression
9796	1B1U.00	Symptoms of depression
6950	E112.13	Endogenous depression first episode
595	E200300	Anxiety with depression
2639	1465	H/0: depression
7604	Eu32.13	[X] Single episode of reactive depression
10667	Eu32400	[X] Mild depression
6546	E113.11	Endogenous depression-recurrent
5879	Eu32z14	[X] Reactive depression NOS
1055	E204.00	Neurotic depression reactive type
18510	Eu32.12	[X] Single episode of psychogenic depression
9183	E11z200	Masked depression
8902	Eu33.13	[X] Recurrent episodes of reactive depression
19696	Eu33.12	[X] Recurrent episodes of psychogenic depression
29527	R007z13	[D] Post-operative depression
6482	E112.12	Endogenous depression first episode
17770	E130.11	Psychotic reactive depression
9083	1285	FH: depression
3716	62T1.00	Puerperal depression
7749	Eu41211	[X] Mild anxiety depression
7737	Eu34113	[X] Neurotic depression
15220	Eu34114	[X] Persistent anxiety depression
2923	E2B0.00	Post viral depression
98252	Eu32600	[X] Major depression moderately severe
24112	Eu32313	[X] Single episode of psychotic depression
2972	E2B1.00	Chronic depression
22806	Eu32212	[X] Single episode major depression without psychotic symptoms
98417	Eu32800	[X] Major depression severe with psychotic symptom
56609	Eu32y12	[X] Single episode of masked depression NOS
11252	Eu33212	[X] Major depression recurrent without psychotic symptoms
11329	Eu33211	[X] Endogenous depression without psychotic symptom
10720	Eu32y11	[X] Atypical depression
32941	Eu33313	[X] Recurrent severe episodes/major depression psychotic symptom
4979	E112.11	Agitated depression
28248	Eu32z13	[X] Prolonged single episode of reactive depression
13267	12G3.00	FH: Puerperal depression
98414	Eu32700	[X] Major depression severe without psychotic symptoms

(Continued) Appendix 13 Read code list of psychiatric conditions

Depression		
Medcode	**Read code**	**Term**
73991	Eu33214	[X] Vital depression recurrent without psychotic symptoms
23731	Eu33311	[X] Endogenous depression with psychotic symptoms
16861	Eu33315	[X] Recurrent severe episodes of psychotic depression
59386	Eu32213	[X] Single episode vital depression without psychotic symptoms
24117	Eu32311	[X] Single episode of major depression and psychotic symptoms
Anxiety		
Medcode	**Read code**	**Term**
1758	E200400	Chronic anxiety
636	E200.00	Anxiety states
655	E200300	Anxiety with depression
4534	E200z00	Anxiety state NOS
11913	Eu41200	[X] Mixed anxiety and depressive disorder
13246	1288	FH: Anxiety state
3407	1466	H/O: Anxiety state
5385	Eu41.00	[X] Other anxiety disorders
962	Eu41111	[X] Anxiety neurosis
9386	Eu40.00	[X] Phobic anxiety disorders
4634	E200500	Recurrent anxiety
6939	E200000	Anxiety state unspecified
4659	E200200	Generalised anxiety disorder
25638	Eu41z11	[X] Anxiety NOS
23838	Eu41z00	[X] Anxiety disorder, unspecified
10344	Eu41100	[X] Generalized anxiety disorder
7749	Eu41211	[X] Mild anxiety depression
15220	Eu34114	[X] Persistent anxiety depression
17687	Eu51511	[X] Dream anxiety disorder
28167	Eu41y11	[X] Anxiety hysteria
9944	E20.12	Phobic anxiety
20773	Eu05400	[X] Organic anxiety disorder
50191	Eu4113	[x] Anxiety state
35825	Eu41112	[X] Anxiety reaction
34064	Eu40z00	[X] Phobic anxiety disorder unspecified
24066	E41y00	[X] Other specified anxiety disorders
44321	Eu41300	[X] Other mixed anxiety disorders
Personality disorder		
Medcode	**Read code**	**Term**
1364	E21y500	Immature personality disorder
2076	E21..00	Personality disorders

(Continued) Appendix 13 Read code list of psychiatric conditions

Personality disorder		
Medcode	**Read code**	**Term**
3369	E212.00	Schizoid personality disorder
4515	E216.00	Inadequate personality disorder
5652	E210.00	Paranoid personality disorder
7745	EU60300	[X] Emotionally unstable personality disorder
10290	Eu34112	[X] Depressive personality disorder
10455	E211200	Depressive personality disorder
15098	E21z.00	Personality disorder NOS
18565	E21y200	Borderline personality disorder
20839	Eiu60311	[X] Aggressive personality disorder
27481	E215.00	Histrionic personality disorder
27803	E21y400	Eccentric personality disorder
27945	Eu60411	[X] Hysterical personality disorder
30603	Eu61.00	[X] Mixed and other personality disorder
31789	Eu60312	[X] Borderline personality disorder
43690	Eu60400	[X] Histrionic personality disorder
49600	Eu60y00	[X] Other specific personality disorder
52465	Eu60500	[X] Anankastic personality disorder
58693	Eu60313	[X] Explosive personality disorder
69185	Eu60412	[X] Psychoinfantile personality disorder
Psychoses		
Medcode	**Read code**	**Term**
2882	E00z.00	Senile or presenile psychoses NOS
14656	E11..00	Affective psychoses
55150	E03..00	Transient organic psychoses
15958	E1.00	Non-organic psychoses
31984	E13..00	Other nonorganic psychoses
11597	N083C00	Unspecified manic-depressive psychoses
16256	E02..00	Drug psychoses
51135	E02y.00	Other drug psychoses
60178	E11y.00	Other and unspecified manic-depressive psychoses
20228	E13..11	Reactive psychoses
Schizophrenia		
Medcode	**Read code**	**Term**
6325	1464	H/0: schizophrenia
8407	E10z.00	Schizophrenia
15733	E100000	Unspecified schizophrenia
21986	Eu05200	[X] Organic delusional schizophrenia
34966	Eu20z00	[X] Schizophrenia unspecified
35848	Eu20600	[X] Simple schizophrenia

(Continued) Appendix 13 Read code list of psychiatric conditions

Schizophrenia		
Medcode	**Read code**	**Term**
43800	7606y00	Chronic schizo-affective schizophrenia
49852	Eu21.16	[X] Pseudoneurotic schizophrenia
51322	E103300	Acute exacerbation of subchronic paranoid schizophrenia
53032	E103400	Acute exacerbation of chronic paranoid schizophrenia
64264	Eu20500	[X] Residual schizophrenia
91547	Eu20311	[X] Atypical schizophrenia
92994	E10y.11	Cenesthopathic schizophrenia
94299	E105200	Chronic latent schizophrenia
99000	E107.11	Cyclic Schizophrenia
104760	E103100	Subchronic paranoid schizophrenia
104763	Eu25211	[X] Cyclic schizophrenia
Paranoia		
Medcode	**Read code**	**Term**
30404	E015.00	Alcoholic paranoia
45997	E021.00	Drug-induced paranoia or hallucinatory states
55236	Eu22y13	[X] Paranoia querulans
Neurosis		
Medcode	**Read code**	**Term**
5678	Eu203000	Compulsive neurosis
8584	Eu34111	[X] Depressive neurosis
24251	Eu42.11	[X] Anankastic neurosis
57567	Eu60z11	[X] Character neurosis NOS
72171	E20y300	Psychasthenic neurosis
100105	7NC6A00	[SO] Plantar aponeurosis
Insomnia and hallucinations		
Medcode	**Read code**	**Term**
5675	1B1B100	Middle insomnia
30626	B67z.00	[X] Nonorganic insomnia
48539	R005100	[D] Insomnia with sleep apnoea
2455	R001.00	[D] Hallucinations
53761	Ryu5300	[X] Other hallucinations

Appendix 14 Regression analysis of associates with missing variables

	Marital	Townsend	Smoking	Alcohol
Variables	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Age (years)	1.01 (1.00-1.01)*	1.00 (1.00-1.00)*	1.00 (1.00-1.01)*	1.01 (1.00-1.01)*
Gender	0.72 (0.70-0.74)*	0.97 (0.94-0.99)*	0.93 (0.91-0.98)*	1.20 (1.17-1.23)*
Region	0.97 (0.97-0.97)*	1.45 (1.44-1.45)*	0.98 (0.98-0.98)*	1.00 (1.00-1.00)
Pain diagnosis				
Osteoarthritis	0.96 (0.93-.099)*	1.14 (1.10-1.17)*	0.76 (0.74-0.78)*	0.77 (0.74-0.79)*
Fibromyalgia	1.04 (0.96-1.14)	1.40 (1.28-1.52)*	0.96 (0.89-1.04)	0.99 (0.92-1.06)
Back pain	1.03 (1.00-1.06)	1.01 (0.98-1.04)	0.77 (0.75-0.79)*	0.81 (0.79-0.83)*
Shoulder pain	0.97 (0.94-1.00)*	0.97 (0.94-1.01)	0.86 (0.84-0.88)*	0.85 (0.83-0.87)*
Neck pain	1.00 (0.97-1.03)	0.99 (0.96-1.02)	0.85 (0.83-0.88)*	0.87 (0.85-0.90)*
Sciatica	0.95 (0.91-0.98)*	0.98 (0.94-1.01)	0.85 (0.82-0.87)	0.81 (0.78-0.83)*
Thoracic pain	1.03 (1.00-1.06)	0.99 (0.96-1.02)	0.90 (0.87-0.92)*	0.89 (0.86-0.91)*
Neuropathy	0.92 (0.87-0.98)*	1.02 (0.95-1.08)	0.93 (0.88-0.98)*	0.95 (0.90-1.01)
Head	1.04 (1.00-1.08)*	0.98 (0.94-1.01)	0.91 (0.88-0.94)*	0.95 (0.92-0.98)*
Migraine	0.90 (0.85-0.95)*	0.97 (0.91-1.03)	0.89 (0.84-0.94)*	0.87 (0.83-0.92)*
Abdominal pain	0.99 (0.96-1.02)	1.03 (1.00-1.06)	0.91 (0.89-0.93)*	0.87 (0.85-0.89)*
Unspecified arthritis	1.03 (0.98-1.07)	1.14 (1.09-1.19)*	0.98 (0.94-1.02)	0.90 (0.87-0.94)*
Rheumatoid arthritis	0.96 (0.67-1.36)	0.69 (0.48-0.97)*	1.43 (1.04-1.97)*	1.52 (1.12-2.07)*
Ankylosing spondylitis	1.11 (0.90-1.37)	0.93 (0.76-1.15)	0.93 (0.78-1.12)	0.90 (0.75-1.07)
Lupus	0.96 (0.79-1.18)	1.13 (0.92-1.39)	0.80 (0.66-0.96)*	0.87 (0.73-1.05)
Psoriatric arthritis	0.94 (0.78-1.13)	1.30 (1.08-1.57)*	0.94 (0.79-1.11)	0.96 (0.82-1.14)
Colitis	0.90 (0.81-0.99)*	0.99 (0.89-1.10)	1.07 (0.98-1.18)	0.97 (0.88-1.06)
Crohn's disease arthritis	1.00 (0.86-1.16)	1.10 (0.95-1.29)	0.92 (0.80-1.05)	0.98 (0.86-1.11)
Gout	1.13 (0.83-1.53)	1.09 (0.81-1.45)	1.02 (0.79-1.33)	0.72 (0.56-0.93)*
Pancreatitis	1.01 (0.91-1.13)	1.03 (0.92-1.15)	0.85 (0.77-0.94)*	0.91 (0.83-1.00)*
Spinal pain	0.90 (0.83-0.97)*	0.85 (0.78-0.92)*	1.00 (0.93-1.48)	0.92 (0.86-0.98)*
Cervical spondylosis	0.82 (0.65-1.02)*	1.01 (0.80-1.28)	1.20 (0.97-1.48)	0.99 (0.80-1.21)
Postherpetic neuralgia	0.99 (0.88-1.11)	0.94 (0.83-1.05)	0.92 (0.83-1.02)	0.84 (0.76-0.93)*
Phantom limb pain	1.01 (0.80-1.27)	0.91 (0.72-1.15)	1.06 (0.87-1.29)	1.25 (1.03-1.52)*
Complex regional pain syndrome	0.82 (0.55-1.22)	0.75 (0.49-1.15)	0.81 (0.55-1.20)	0.92 (0.63-1.33)
Trigeminal neuralgia	0.98 (0.88-1.11)	1.08 (0.96-1.21)	0.95 (0.85-1.06)	0.90 (0.81-0.99)*
Facial pain	0.97 (0.90-1.05)	0.96 (0.88-1.04)	0.92 (0.86-0.99)*	0.97 (0.90-1.03)
Temporomandibular joint disorder	0.98 (0.89-1.08)	0.95 (0.86-1.05)	0.94 (0.86-1.03)	0.93 (0.86-1.01)
Gallstones	1.05 (0.90-1.22)	0.93 (0.80-1.08)	0.92 (0.80-1.05)	1.08 (0.95-1.22)

*Significance at $p \leq 0.05$

(Continued) Appendix 14 Regression analysis of associates with missing variables

	Marital status	Townsend	Smoking	Alcohol
Variable	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Pain diagnosis				
Menstrual pain	1.25 (0.78-2.01)	0.49 (0.30-0.82)*	0.84 (0.55-1.29)	1.09 (0.73-1.64)
Pelvic pain	0.95 (0.84-1.07)	0.92 (0.81-1.05)	0.95 (0.85-1.07)	0.89 (0.80-0.99)*
Postoperative pain	0.90 (0.82-0.98)*	1.03 (0.94-1.13)	0.87 (0.80-0.94)*	0.82 (0.76-0.89)*
Cervical pain	0.95 (0.84-1.07)	1.31 (1.16-1.48)*	1.06 (0.95-1.18)	0.95 (0.85-1.05)
QOF Comorbidities				
Hypertension	1.01 (0.98-1.05)	0.99 (0.96-1.02)	0.68 (0.66-0.70)*	0.66 (0.64-0.68)*
Coronary kidney disease	0.91 (0.87-0.94)*	0.96 (0.92-0.99)*	0.74 (0.72-0.77)*	0.83 (0.80-0.86)*
Coronary heart disease	0.94 (0.90-0.98)*	1.13 (1.08-1.18)*	0.99 (0.96-1.03)	0.74 (0.72-0.77) *
Diabetes	1.04 (1.00-1.09)*	0.96 (0.92-1.00)*	0.98 (0.94-1.02)	0.87 (0.84-0.91)*
Asthma	1.01 (0.97-1.05)	0.94 (0.91-0.98)*	0.79 (0.77-0.82)*	0.89 (0.86-0.92)*
Osteoporosis	0.93 (0.89-0.97)*	1.07 (1.02-1.12)*	0.87 (0.83-0.90)*	0.87 (0.84-0.90)*
COPD	1.00 (0.95-1.05)	1.06 (1.01-1.11)*	1.05 (1.00-1.09)*	0.95 (0.91-0.99)*
Stroke	0.95 (0.90-0.99)*	1.03 (0.98-1.08)*	0.94 (0.90-0.98)*	0.96 (0.92-1.00)*
Heart failure	0.95 (0.91-1.00)	1.01 (0.96-1.07)	1.13 (1.08-1.19)*	1.00 (0.96-1.05)
Atrial fibrillation	0.97 (0.92-1.02)	0.96 (0.91-1.01)	0.85 (0.81-0.89)*	0.83 (0.79-0.87)*
Hypothyroidism	1.04 (0.99-1.10)	0.94 (0.90-0.99)*	0.88 (0.84-0.92)*	0.93 (0.89-0.97)*
Learning disability	1.28 (0.87-1.88)	0.91 (0.63-1.30)	0.57 (0.41-0.79)*	1.78 (1.27-2.50)*
Epilepsy	0.98 (0.91-1.07)	1.03 (0.95-1.12)	0.91 (0.85-0.97)*	1.00 (0.94-1.07)
Mental health disorder	1.00 (0.91-1.11)	0.78 (0.71-0.87)*	0.82 (0.75-0.89)*	0.90 (0.83-0.99)*
Dementia	1.05 (0.98-1.11)	1.10 (1.04-1.17)*	0.88 (0.84-0.93)*	1.33 (1.26-1.40)*
Rheumatoid arthritis	1.06 (0.74-1.50)*	1.44 (1.02-2.05)*	0.69 (0.50-0.94)*	0.68 (0.50-0.93)*
Obesity	0.72 (0.68-0.77)*	1.13 (1.07-1.21)*	0.81 (0.77-0.86)*	0.78 (0.74-0.83)*
Psychiatric disorders				
Personality disorder	1.13 (0.97-1.31)	0.94 (0.82-1.09)	1.06 (0.94-1.20)	1.13 (1.00-1.28)*
Insomnia & hallucination	1.21 (0.87-1.68)	1.88 (1.36-2.60)*	0.97 (0.74-1.27)	0.82 (0.63-1.07)
Psychosis	0.74 (0.5101.06)	1.22 (0.84-1.76)	1.89 (1.36-2.62)*	0.85 (0.61-1.18)
Paranoia	1.26 0.80-1.98)	0.72 (0.47-1.10)	1.34 (0.94-1.91)	0.95 (0.67-1.36)
Neurosis	0.82 (0.56-1.21)	1.36 (0.91-2.05)	1.06 (0.74-1.53)	0.99 (0.70-1.41)
Schizophrenia	1.09 (0.62-1.93)	1.74 (1.00-3.00)*	0.79 (0.48-1.30)	0.91 (0.57-1.45)
Depression	0.97 (0.94-1.01)	1.02 (0.98-1.06)	0.69 (0.67-0.71)*	0.69 (0.67-0.71)*
Anxiety	1.01 (0.97-1.05)	1.15 (1.11-1.20)*	0.85 (0.83-0.88)*	0.88 (0.86-0.91)*
Co-prescriptions				
Antidepressants	0.96 (0.94-0.99)*	0.98 (0.95-1.00)	1.27 (1.24-1.30)*	1.23 (1.19-1.26)*
Benzodiazepines	0.96 (0.93-0.99)*	1.08 (0.93-1.01)*	1.30 (1.27-1.34)*	1.28 (1.24-1.31)*
Non-benzodiazepines	0.99 (0.95-1.03)	0.97 (0.93-1.01)	1.22 (1.17-1.26)*	1.23 (1.19-1.28)*

*Significance at $p \leq 0.05$

Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Non-steroidal anti-inflammatory drugs			
Product code	**Drug**	**Strength**	**Formulation**
526	Aceclofenac	100mg	Tablet
9474	Aceclofenac	100mg	Tablet
344	Acemetacin	60mg	Capsule
2258	Acemetacin	60mg	Capsule
474	Celecoxib	100mg	Capsule
5080	Celecoxib	200mg	Capsule
5175	Celecoxib	100mg	Capsule
5254	Celecoxib	200mg	Capsule
5173	Dexketoprofen trometamol	25mg	Tablet
9637	Dexketoprofen trometamol	25mg	Tablet
10325	Dexibuprofen	300mg	Tablet
11907	Dexibuprofen	400mg	Tablet
21419	Dexibuprofen	300mg	Tablet
21421	Dexibuprofen	400mg	Tablet
40	Diclofenac sodium	50mg	Gastro-resistant tablet
156	Diclofenac diethylammonium	10mg/1gram	Gel
417	Diclofenac sodium	50mg	Dispersible tablet
447	Diclofenac sodium	75mg	MR-capsule
497	Diclofenac sodium	25mg	Gastro-resistant tablet
499	Diclofenac sodium	50mg	Suppository
580	Diclofenac sodium	75mg	Modified-release tablet
589	Diclofenac sodium	50mg	Dispersible tablet
597	Diclofenac potassium	50mg	Tablet
628	Diclofenac potassium	25mg	Tablet
649	Diclofenac sodium	25mg	Gastro-resistant tablet
827	Diclofenac diethylammonium	10mg/1gram	Gel
917	Diclofenac Sodium	50mg	Tablets
928	Diclofenac Sodium	25mg	Tablets
1075	Diclofenac Sodium	50mg	Ec Tablets
1115	Diclofenac sodium	100mg	Modified-release capsule
1116	Diclofenac sodium	100mg	Suppository
1139	Diclofenac sodium	25mg	Gastro-resistant tablet
1233	Diclofenac Sodium	75mg	Modified Release Tablet
1984	Diclofenac Sodium	100mg	Modified Release Tablet
2386	Diclofenac sodium	100mg	Modified-release tablet
2904	Diclofenac sodium	75mg	Modified-release capsule
3416	Diclofenac sodium	100mg	Modified-release tablet
3421	Diclofenac sodium	75mg	Modified-release capsule
3852	Diclofenac sodium	100mg	Modified-release capsule

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Non-steroidal anti-inflammatory drugs			
Product code	**Drug**	**Strength**	**Formulation**
3958	Diclofenac sodium	25mg	Suppository
4506	Diclofenac sodium	75mg	Modified-release tablet
4625	Diclofenac sodium	75mg	Modified-release tablet
4631	Diclofenac sodium	50mg	Gastro-resistant tablet
4692	Diclofenac sodium	50mg	Gastro-resistant tablet
4806	Diclofenac sodium	100mg	Suppository
5085	Diclofenac potassium	50mg	Tablet
5200	Diclofenac sodium	50mg	Suppository
5401	Diclofenac potassium	25mg	Tablet
6208	Diclofenac diethylammonium	10mg/1gram	Gel
6435	Diclofenac sodium	16mg/1ml	Liquid
7667	Diclofenac sodium	12.5mg	Suppository
8062	Diclofenac sodium	75mg	Modified-release capsule
8789	Diclofenac sodium	100mg	Modified-release tablet
9222	Diclofenac sodium	75mg	Modified-release tablet
9500	Diclofenac sodium	75mg	Modified-release tablet
11168	Diclofenac sodium	100mg	Modified-release tablet
11322	Diclofenac sodium	75mg	Modified-release tablet
11522	Diclofenac sodium	16mg/1ml	Liquid
11540	Diclofenac sodium	16mg/1ml	Liquid
14084	Diclofenac sodium	75mg	Modified-release tablet
14672	Diclofenac sodium	75mg	Modified-release tablet
14707	Diclofenac sodium	100mg	Modified-release tablet
14884	Diclofenac epolamine	10mg/1gram	Transdermal patch
14901	Diclofenac epolamine	10mg/1gram	Transdermal patch
16222	Diclofenac sodium	50mg	Gastro-resistant tablet
16272	Diclofenac sodium	100mg	Modified-release tablet
16286	Diclofenac sodium	75mg	Modified-release tablet
17029	Diclofenac sodium	75mg	Modified-release tablet
17030	Diclofenac sodium	75mg	Modified-release capsule
17126	Diclofenac sodium	75mg	Modified-release tablet
17128	Diclofenac sodium	50mg	Gastro-resistant tablet
17491	Diclofenac sodium	75mg	Modified-release tablet
17525	Diclofenac sodium	100mg	Modified-release tablet
18448	Diclofenac sodium	12.5mg	Suppository
18798	Diclofenac sodium	50mg	Gastro-resistant tablet
20621	Diclofenac sodium	75mg	Modified-release tablet
20805	Diclofenac sodium	75mg	Modified-release tablet
21387	Diclofenac sodium	50mg	Gastro-resistant tablet

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Non-steroidal anti-inflammatory drugs			
Product code	**Drug**	**Strength**	**Formulation**
21610	Diclofenac sodium	100mg	Modified-release tablet
21824	Diclofenac sodium	50mg	Gastro-resistant tablet
24122	Diclofenac sodium	50mg	Gastro-resistant tablet
25329	Diclofenac sodium	25mg	Gastro-resistant tablet
26165	Diclofenac sodium	50mg	Gastro-resistant tablet
26351	Diclofenac sodium	75mg	Modified-release tablet
26631	Diclofenac sodium	100mg	Modified-release capsule
28553	Diclofenac sodium	50mg	Gastro-resistant tablet
29181	Diclofenac sodium	75mg	Modified-release tablet
29330	Diclofenac sodium	50mg	Gastro-resistant tablet
30297	Diclofenac sodium	50mg	Gastro-resistant tablet
30923	Diclofenac sodium	100mg	Suppository
31589	Diclofenac sodium	75mg	Modified-release tablet
32854	Diclofenac sodium	75mg	Modified-release capsule
33645	Diclofenac sodium	75mg	Modified-release tablet
33994	Diclofenac sodium	25mg	Gastro-resistant tablet
34091	Diclofenac sodium	25mg	Gastro-resistant tablet
34212	Diclofenac sodium	75mg	Modified-release tablet
35893	Diclofenac sodium	100mg	Modified-release tablet
38881	Diclofenac sodium	75mg	Modified-release capsule
38948	Diclofenac sodium	100mg	Modified-release capsule
38992	Diclofenac sodium	75mg	Modified-release tablet
42793	Diclofenac sodium	100mg	Modified-release tablet
162	Diclofenac sodium/Misoprostol	50mg +200mcg	Gastro-resistant tablet
1692	Diclofenac sodium/Misoprostol	50mg +200mcg	Gastro-resistant tablet
2387	Diclofenac sodium/Misoprostol	75mg +200mcg	Gastro-resistant tablet
4880	Diclofenac sodium/Misoprostol	75mg +200mcg	Gastro-resistant tablet
162	Diclofenac sodium/Misoprostol	50mg +200mcg	Gastro-resistant tablet
1692	Diclofenac sodium/Misoprostol	50mg +200mcg	Gastro-resistant tablet
2387	Diclofenac sodium/Misoprostol	75mg +200mcg	Gastro-resistant tablet
4880	Diclofenac sodium/Misoprostol	75mg +200mcg	Gastro-resistant tablet
5266	Etodolac	600mg	Modified-release tablet
5455	Etodolac	600mg	Modified-release tablet
10033	Etodolac	300mg	Capsule
24356	Etodolac	300mg	Capsule
38770	Etodolac	600mg	Modified-release tablet
650	Etoricoxib	60mg	Tablet
5812	Etoricoxib	90mg	Tablet
5938	Etoricoxib	120mg	Tablet

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Non-steroidal anti-inflammatory drugs			
Product code	**Drug**	**Strength**	**Formulation**
6464	Etoricoxib	60mg	Tablet
6498	Etoricoxib	90mg	Tablet
9822	Etoricoxib	120mg	Tablet
37562	Etoricoxib	30mg	Tablets
37587	Etoricoxib	30mg	Tablets
4469	Fenoprofen calcium	300mg	Tablet
10678	Fenoprofen calcium	300mg	Tablet
2366	Flurbiprofen	100mg	Tablet
3182	Flurbiprofen	50mg	Tablet
3266	Flurbiprofen	50mg	Tablet
4043	Flurbiprofen	200mg	Modified-release capsule
6249	Flurbiprofen	100mg	Tablet
9439	Flurbiprofen	200mg	Modified-release capsule
38944	Flurbiprofen	200mg	Modified-release capsule
15	Ibuprofen	400mg	Tablet
332	Ibuprofen	50mg/1gram	Gel
360	Ibuprofen	20mg/1ml	Oral suspension
392	Ibuprofen	200mg	Modified-release capsule
402	Ibuprofen	200mg	Tablet
407	Ibuprofen	600mg	Effervescent granules
416	Ibuprofen	200mg	Tablet
586	Ibuprofen	200mg	Capsule
647	Ibuprofen	20mg/1ml	Oral suspension
784	Ibuprofen	300mg	Modified-release capsule
1086	Ibuprofen	600mg	Tablet
1156	Ibuprofen	50mg/1gram	Gel
1270	Ibuprofen	50mg/1gram	Gel
1392	Ibuprofen	800mg	Modified-release tablet
1739	Ibuprofen	400mg	Tablet
2129	Ibuprofen	800mg	Modified-release tablet
2938	Ibuprofen	100mg/5ml	Oral Suspension
3599	Ibuprofen	600mg	Effervescent granules
4216	Ibuprofen	600mg	Tablet
4648	Ibuprofen	50mg/1ml	Spray
4731	Ibuprofen	100mg/5ml	Oral Suspension
5648	Ibuprofen	200mg	Orodispersible tablet
5767	Ibuprofen	100mg/1gram	Gel
5896	Ibuprofen	100mg/1gram	Gel
7058	Ibuprofen	100mg/5ml	Oral Suspension

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Non-steroidal anti-inflammatory drugs			
Product code	**Drug**	**Strength**	**Formulation**
7141	Ibuprofen	100mg/1gram	Gel
7261	Ibuprofen	50mg/1gram	Gel
7535	Ibuprofen	200mg	Capsule
8510	Ibuprofen	50mg/1ml	Spray
10149	Ibuprofen	200mg	Capsule
10265	Ibuprofen	50mg/1gram	Gel
10785	Ibuprofen	300mg	Modified-release capsule
11550	Ibuprofen	200mg	Orodispersible tablet
11554	Ibuprofen/Codeine phosphate	200mg +12.8mg	Tablet
13083	Ibuprofen/Levomenthol	50mg/1gram + 30mg/1gram	Gel
13893	Ibuprofen/Codeine phosphate	200mg +12.8mg	Tablet
14333	Ibuprofen	400mg	Capsule
15767	Ibuprofen	50mg/1gram	Foam
15930	Ibuprofen/Levomenthol	50mg/1gram + 30mg/1gram	Gel
19046	Ibuprofen	400mg	Tablet
20967	Ibuprofen	50mg/1gram	Gel
24086	Ibuprofen	50mg/1gram	Gel
26159	Ibuprofen	100mg/1gram	Gel
31054	Ibuprofen	100mg/1gram	Gel
35890	Ibuprofen	200mg	Tablet
37972	Ibuprofen	50mg/1gram	Gel
38332	Ibuprofen	200mg	Tablet
39019	Ibuprofen	800mg	Modified-release tablet
39873	Ibuprofen	400mg	Tablet
120	Indometacin	25mg	Capsule
920	Indometacin	100mg	Suppository
1210	Indometacin	75mg	Modified-release capsule
1496	Indometacin	75mg	Modified-release capsule
17680	Indometacin	75mg	Modified-release capsule
18662	Indometacin	75mg	Modified-release capsule
389	Ketoprofen	50mg	Capsule
838	Ketoprofen	200mg	Modified-release capsule
1231	Ketoprofen	100mg	Capsule
1571	Ketoprofen	100mg	Modified-release capsule
2606	Ketoprofen	25mg/1gram	Gel
3043	Ketoprofen	200mg	Modified-release capsule
3077	Ketoprofen	25mg/1gram	Gel

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Non-steroidal anti-inflammatory drugs			
Product code	**Drug**	**Strength**	**Formulation**
3326	Ketoprofen	100mg	Modified-release capsule
3336	Ketorolac trometamol	10mg	Tablet
8385	Ketoprofen	150mg	Modified-release capsule
9421	Ketoprofen	25mg/1gram	Gel
12000	Ketoprofen	100mg	Suppository
15286	Ketoprofen	200mg	Modified-release capsule
16637	Ketorolac trometamol	10mg	Tablet
40185	Ketoprofen	200mg	Modified-release capsule
41364	Ketoprofen/omeprazole	100mg +20mg	Modified Release Capsules
41366	Ketoprofen/omeprazole	100mg +20mg	Modified Release Capsules
126	Mefenamic acid	250mg	Capsule
259	Mefenamic acid	250mg	Capsule
296	Mefenamic acid	500mg	Tablet
1073	Mefenamic acid	500mg	Tablet
9736	Mefenamic acid	10mg/1ml	Oral suspension
13459	Mefenamic acid	500mg	Tablet
21831	Mefenamic acid	250mg	Capsule
754	Meloxicam	7.5mg	Suppository
850	Meloxicam	7.5mg	Tablet
1469	Meloxicam	15mg	Tablet
1470	Meloxicam	15mg	Tablet
2243	Meloxicam	7.5mg	Tablet
3170	Meloxicam	15mg	Suppository
11970	Meloxicam	7.5mg	Suppository
13627	Meloxicam	15mg	Suppository
35935	Meloxicam	7.5mg	Tablet
2234	Nabumetone	500mg	Tablet
2235	Nabumetone	500mg	Tablet
11466	Nabumetone	100mg/1ml	Oral suspension
140	Naproxen	500mg	Suppository
661	Naproxen	250mg	Tablet
807	Naproxen	500mg	Tablet
1043	Naproxen sodium	275mg	Tablet
1866	Naproxen	500mg	Tablet
2288	Naproxen	250mg	Tablet
3053	Naproxen	500mg	Gastro-resistant tablet
3431	Naproxen	250mg	Gastro-resistant tablet
3432	Naproxen	375mg	Gastro-resistant tablet
3817	Naproxen sodium	275mg	Tablet

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Non-steroidal anti-inflammatory drugs			
Product code	**Drug**	**Strength**	**Formulation**
3901	Naproxen	500mg	Gastro-resistant tablet
3972	Naproxen	250mg	Gastro-resistant tablet
4045	Naproxen	375mg	Gastro-resistant tablet
5268	Naproxen sodium	500mg	Modified-release tablet
5407	Naproxen	25mg/1ml	Oral suspension
21840	Naproxen	250mg	Tablet
34290	Naproxen	250mg	Gastro-resistant tablet
39693	Naproxen	200mg/5ml	Oral Suspension
141	Piroxicam	10mg	Capsule
341	Piroxicam	10mg	Capsule
1755	Piroxicam	20mg	Capsule
3409	Piroxicam	20mg	Orodispersible tablet
3710	Piroxicam	20mg	Dispersible tablet
3935	Piroxicam	20mg	Capsule
4965	Piroxicam	20mg	Orodispersible tablet
10169	Piroxicam betadex	20mg	Tablet
11495	Piroxicam betadex	20mg	Tablet
39109	Piroxicam	20mg	Orodispersible tablet
41365	Ketoprofen/Omeprazole	20mg +200mg	Modified-release capsule
41367	Ketoprofen/Omeprazole	20mg +200mg	Modified-release capsule
3897	Sulindac	100mg	Tablet
5482	Sulindac	200mg	Tablet
3974	Tenoxicam	20mg	Tablet
12075	Tenoxicam	20mg	Tablet
1778	Tiaprofenic acid	300mg	Tablet
2863	Tiaprofenic acid	300mg	Tablet
14776	Tiaprofenic acid	300mg	Tablet
7222	Tolfenamic acid	200mg	Tablet
14994	Tolfenamic acid	200mg	Tablet
Tramadol			
Product code	**Drug**	**Strength**	**Formulation**
86	Tramadol hydrochloride	50mg	Capsule
187	Tramadol hydrochloride	50mg	Capsule
687	Paracetamol/Tramadol hydrochloride	325mg+ 37.5mg	Tablet
701	Tramadol hydrochloride	50mg	Modified-release capsule
3378	Tramadol hydrochloride	50mg	Soluble tablet
3644	Tramadol hydrochloride	100mg	Modified-release tablet
4114	Tramadol hydrochloride	100mg	Modified-release capsule

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Tramadol			
Product code	**Drug**	**Strength**	**Formulation**
4115	Tramadol hydrochloride	100mg	Modified-release tablet
4834	Tramadol hydrochloride	150mg	Modified-release capsule
4999	Tramadol Hydrochloride	150mg	Modified-release Tablet
5028	Tramadol Hydrochloride	200mg	Modified-release Tablet
5169	Tramadol hydrochloride	200mg	Modified-release tablet
5257	Tramadol Hydrochloride	150mg	Modified-release Tablet
6153	Tramadol hydrochloride	150mg	Modified-release tablet
6215	Tramadol hydrochloride	200mg	Modified-release capsule
6558	Paracetamol/Tramadol hydrochloride	325mg+ 37.5mg	Tablet
8416	Tramadol Hydrochloride	200mg	Modified-release Tablet
9389	Tramadol hydrochloride	50mg	Modified-release capsule
9396	Tramadol hydrochloride	100mg	Modified-release capsule
11101	Tramadol hydrochloride	50mg	Soluble tablet
11734	Tramadol hydrochloride	50mg	Orodispersible tablet
11746	Tramadol hydrochloride	300mg	Modified-release tablet
11748	Tramadol hydrochloride	400mg	Modified-release tablet
13813	Tramadol hydrochloride	50mg	Capsule
14490	Tramadol hydrochloride	50mg	Capsule
16076	Paracetamol/Tramadol hydrochloride	325mg+ 37.5mg	Tablets
16271	Tramadol hydrochloride	300mg	Modified-release tablet
16395	Tramadol hydrochloride	200mg	Modified-release tablet
19993	Tramadol hydrochloride	100mg	Modified-release tablet
20310	Tramadol hydrochloride	50mg	Orodispersible tablet
21397	Tramadol hydrochloride	400mg	Modified-release tablet
21777	Tramadol hydrochloride	200mg	Modified-release tablet
21797	Tramadol hydrochloride	200mg	Modified-release capsule
21947	Tramadol hydrochloride	150mg	Modified-release tablet
23981	Tramadol hydrochloride	150mg	Modified-release capsule
26986	Tramadol hydrochloride	200mg	Modified-release tablet
27591	Tramadol hydrochloride	150mg	Modified-release tablet
28728	Tramadol hydrochloride	300mg	Modified-release tablet
29860	Tramadol hydrochloride	50mg	Capsule
32165	Tramadol hydrochloride	50mg	Capsule
34260	Tramadol hydrochloride	100mg	Modified-release tablet
34281	Tramadol Hydrochloride	200mg	Modified-release Tablet
34422	Tramadol hydrochloride	50mg	Capsule
34570	Tramadol hydrochloride	50mg	Capsule
35347	Tramadol Hydrochloride	100mg	Modified-release Tablet

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Tramadol			
Product code	**Drug**	**Strength**	**Formulation**
35651	Tramadol hydrochloride	200mg	Modified-release tablet
35656	Tramadol hydrochloride	100mg	Modified-release tablet
35806	Tramadol hydrochloride	100mg	Modified-release tablet
36035	Tramadol hydrochloride	300mg	Modified-release tablet
36732	Tramadol Hydrochloride	50mg	12-Hour Modified Release Tablets
36873	Tramadol hydrochloride	50mg	Modified-release tablet
37021	Tramadol hydrochloride	200mg	Modified-release tablet
39505	Tramadol hydrochloride	100mg	Modified-release tablet
39709	Tramadol hydrochloride	200mg	Modified-release tablet
39750	Tramadol hydrochloride	150mg	Modified-release tablet
39811	Tramadol hydrochloride	200mg	Modified-release capsule
40058	Tramadol hydrochloride	100mg	Modified-release tablet
40060	Tramadol hydrochloride	200mg	Modified-release tablet
40249	Tramadol hydrochloride	100mg	Modified-release capsule
40254	Tramadol hydrochloride	50mg	Modified-release capsule
42332	Paracetamol/Tramadol hydrochloride	325mg+ 37.5mg	Effervescent tablet
Weak opioids			
Product code	**Drug**	**Strength**	**Formulation**
11	Paracetamol/Dihydrocodeine tartrate	500mg +10mg	Tablet
19	Paracetamol/Codeine phosphate	500mg +8mg	Tablet
53	Dihydrocodeine tartrate	30mg	Tablet
57	Codeine phosphate/Paracetamol	8mg +500mg	Effervescent tablet
96	Codeine phosphate/Paracetamol	30mg +500mg	Tablet
191	Dihydrocodeine tartrate	2mg/1ml	Oral solution
625	Codeine phosphate/Paracetamol	8mg +500mg	Capsule
656	Codeine phosphate/Paracetamol	30mg +500mg	Capsule
767	Codeine phosphate/Paracetamol	30mg +500mg	Capsule
800	Codeine phosphate/Paracetamol	30mg +500mg	Capsule
810	Codeine phosphate/Paracetamol	30mg +500mg	Effervescent tablet
1616	Buclizine hydrochloride/Paracetamol/Codeine phosphate	6.25mg+500mg+ 8mg	Tablet
1640	Codeine phosphate/Paracetamol	30mg +500mg	Tablet
2040	Paracetamol/Dihydrocodeine tartrate	500mg +20mg	Tablet
2041	Dihydrocodeine tartrate	60mg	Modified-release tablet
2047	Codeine Phosphate/Aspirin	8mg+400mg	Tablets
2211	Codeine phosphate/Paracetamol	30mg +500mg	Effervescent tablet

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Weak opioids			
Product code	**Drug**	**Strength**	**Formulation**
2555	Dihydrocodeine Tartrate	10mg +500mg	Tablets
2794	Codeine phosphate/Paracetamol	30mg + 500mg	Tablet
2846	Paracetamol/Codeine phosphate	500mg +30mg	Effervescent Tablet
2917	Paracetamol/Codeine phosphate	500mg+30mg	Tablets
3156	Codeine phosphate/Paracetamol	30mg +500mg	Tablet
3185	Paracetamol/Codeine phosphate	500mg +30mg	Capsules
3239	Meptazinol hydrochloride	200mg	Tablet
3435	Codeine phosphate/Paracetamol	30mg +500mg	Effervescent tablet
3698	Dihydrocodeine tartrate	40mg	Tablet
3724	Paracetamol/Codeine phosphate	500mg +8mg	Tablet
4671	Codeine phosphate/Paracetamol	30mg +500mg	Capsules
4823	Dihydrocodeine tartrate	40mg	Tablet
4950	Dihydrocodeine Tartrate	30mg +500mg	Tablets
5955	Paracetamol/Dihydrocodeine tartrate	500mg +30mg	Tablet
6234	Dihydrocodeine tartrate	120mg	Modified-release tablet
6886	Codeine phosphate/Paracetamol	30mg +500mg	Tablets
7063	Dihydrocodeine tartrate/Paracetamol	2mg/1ml+ 100mg/1ml	Oral suspension
7072	Codeine phosphate/Paracetamol	15mg +500mg	Tablet
7518	Aspirin/Codeine Phosphate	400mg +8mg	Dispersible Tablet
7542	Codeine phosphate/Paracetamol	8mg +500mg	Tablets
8246	Codeine phosphate/Paracetamol	8mg +500mg	Effervescent Tablet
8447	Meptazinol hydrochloride	200mg	Tablet
8456	Dihydrocodeine tartrate	60mg	Modified-release tablet
9209	Dihydrocodeine tartrate	90mg	Modified-release tablet
9275	Dihydrocodeine tartrate	120mg	Modified-release tablet
9313	Dihydrocodeine tartrate	90mg	Modified-release tablet
9432	Paracetamol/Codeine phosphate	500mg +8mg	Soluble Tablet
9457	Paracetamol/Codeine phosphate	500mg +8mg	Tablets
9460	Paracetamol/Codeine phosphate	500mg +8mg	Capsules
9462	Paracetamol/Codeine phosphate	500mg +8mg	Effervescent Tablet
9516	Codeine phosphate/Paracetamol	30mg +500mg	Capsule
9562	Dihydrocodeine Tartrate/Paracetamol	30mg+500mg	Effervescent Tablet
9785	Paracetamol/Dihydrocodeine tartrate	500mg +30mg	Tablet
9855	Paracetamol/Dihydrocodeine tartrate	500mg +20mg	Tablet
10023	Dihydrocodeine Tartrate/Paracetamol	20mg +500mg	Tablets
10176	Codeine phosphate/Paracetamol	15mg +500mg	Tablet
10226	Caffeine/Codeine phosphate/Paracetamol	30mg+8mg +500mg	Tablet
11325	Paracetamol/Codeine phosphate	500mg +30mg	Tablets
11665	Codeine phosphate/Paracetamol	30mg +500mg	Tablet

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Weak opioids			
Product code	**Drug**	**Strength**	**Formulation**
9460	Paracetamol/Codeine phosphate	500mg +8mg	Capsules
9462	Paracetamol/Codeine phosphate	500mg +8mg	Effervescent Tablet
9516	Codeine phosphate/Paracetamol	30mg +500mg	Capsule
9562	Dihydrocodeine Tartrate/Paracetamol	30mg+500mg	Effervescent Tablet
9785	Paracetamol/Dihydrocodeine tartrate	500mg +30mg	Tablet
9855	Paracetamol/Dihydrocodeine tartrate	500mg +20mg	Tablet
10023	Dihydrocodeine Tartrate/Paracetamol	20mg +500mg	Tablets
10176	Codeine phosphate/Paracetamol	15mg +500mg	Tablet
10226	Caffeine/Codeine phosphate/Paracetamol	30mg+8mg +500mg	Tablet
11325	Paracetamol/Codeine phosphate	500mg +30mg	Tablets
11665	Codeine phosphate/Paracetamol	30mg +500mg	Tablet
11807	Paracetamol/Codeine phosphate	500mg +12.8mg	Tablets
14688	Dihydrocodeine Tartrate	500mg +10mg	Tablets
14785	Paracetamol/Codeine phosphate	500mg +15mg	Tablets
14912	Codeine phosphate/Paracetamol	8mg+500mg	Capsules
14964	Codeine phosphate/Paracetamol/Caffeine	8mg+500mg+ 30mg	Soluble tablet
15779	Codeine phosphate/Paracetamol	8mg +500mg	Soluble Tablet
16467	Codeine phosphate/Paracetamol	30mg +500mg	Effervescent Tablet
17563	Paracetamol/Codeine phosphate	500mg +12.8mg	Tablet
17917	Dihydrocodeine Tartrate	20mg +500mg	Effervescent Tablet
18221	Codeine phosphate/Paracetamol	15mg +500mg	Tablets
21880	Codeine phosphate/Paracetamol	30mg +500mg	Capsule
28780	Paracetamol/Dihydrocodeine tartrate	500mg +10mg	Tablet
29488	Codeine phosphate/Paracetamol	8mg +500mg	Effervescent tablet
31577	Codeine phosphate/Paracetamol	30mg +500mg	Capsule
32692	Codeine phosphate/Paracetamol	8mg +500mg	Effervescent tablet
32926	Paracetamol/Dihydrocodeine tartrate	500mg +10mg	Tablet
33643	Paracetamol/Codeine phosphate	500mg +8mg	Tablet
33654	Dihydrocodeine tartrate	30mg	Tablet
34008	Dihydrocodeine tartrate	30mg	Tablet
34579	Dihydrocodeine tartrate	30mg	Tablet
34737	Paracetamol/Dihydrocodeine tartrate	500mg +10mg	Tablet
37904	Paracetamol/Codeine phosphate	500mg +12.8mg	Tablet
38950	Paracetamol/Dihydrocodeine tartrate	500mg +30mg	Tablet
38970	Dihydrocodeine tartrate	40mg	Tablet

(Continued) Appendix 15 Product codes of NSAIDs, tramadol, weak opioids and paracetamol

Paracetamol			
Product code	**Drug**	**Strength**	**Formulation**
7	Paracetamol	500mg	Tablet
139	Paracetamol	500mg	Capsule
262	Paracetamol	50mg/1ml	Oral suspension
1147	Paracetamol	120mg/5ml	Oral Suspension
1609	Paracetamol	500mg	Effervescent tablet
1689	Paracetamol	120mg/5ml	Oral Suspension
1862	Paracetamol	500mg/5ml	Suspension Sugar-free
1999	Paracetamol	125mg	Suppository
2344	Paracetamol	120mg	Suppository
3074	Paracetamol	120mg	Soluble tablet
4186	Paracetamol	250mg/5ml	Suspension Sugar-free
4196	Paracetamol	240mg	Suppository
5239	Paracetamol	1gram	Powder
5243	Paracetamol	500mg	Suppository
5323	Paracetamol	250mg	Suppository
6699	Paracetamol	60mg	Suppository
7205	Paracetamol	500mg	Capsule
9712	Paracetamol	250mg	Orodispersible tablet
14899	Paracetamol	250mg	Suppository
15238	Paracetamol	500mg	Tablet
20068	Paracetamol	250mg/5ml	Suspension Sugar-free
23617	Paracetamol	50mg	Powder
23716	Paracetamol	500mg	Tablet
24000	Paracetamol	500mg	Tablet
24075	Paracetamol	500mg	Tablet
27452	Paracetamol	500mg	Effervescent tablet
27459	Paracetamol	500mg	Tablet
28344	Paracetamol	500mg	Tablet
28346	Paracetamol	500mg	Tablet
32839	Paracetamol	500mg	Tablet
33666	Paracetamol	500mg	Tablet
33710	Paracetamol	500mg	Tablet
33826	Paracetamol	500mg	Tablet
34305	Paracetamol	500mg	Tablet
34500	Paracetamol	500mg	Tablet
35679	Paracetamol	500mg	Tablet
42371	Paracetamol	1gram	Tablet

Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antidepressants			
Product code	**Drug**	**Strength**	**Formulation**
49	Amitriptyline hydrochloride	25mg	Tablet
83	Amitriptyline hydrochloride	10mg	Tablet
487	Amitriptyline hydrochloride	25mg	Modified-release capsule
595	Amitriptyline hydrochloride/Perphenazine	25mg+2mg	Tablet
1208	Amitriptyline hydrochloride/Perphenazine	25mg+2mg	Tablet
1453	Amitriptyline hydrochloride/Perphenazine	10mg+2mg	Tablet
1888	Amitriptyline hydrochloride	50mg	Tablet
2486	Amitriptyline hydrochloride	25mg	Modified-release capsule
2525	Amitriptyline Hydrochloride	75mg	Modified Release Capsules
2985	Amitriptyline hydrochloride	50mg	Modified-release capsule
3490	Amitriptyline hydrochloride/Perphenazine	10mg+2mg	Tablet
3777	Amitriptyline Hydrochloride	10mg/5ml	Oral Solution Sugar-free
4682	Amitriptyline hydrochloride	50mg	Modified-release capsule
4690	Amitriptyline hydrochloride	10mg/1ml	Oral solution
6312	Amitriptyline hydrochloride	5mg/1ml	Oral solution
6894	Perphenazine/Amitriptyline Hydrochloride	2mg+ 25mg	Tablets
7751	Amitriptyline hydrochloride	25mg	Tablet
16323	Perphenazine/Amitriptyline Hydrochloride	2mg+10mg	Tablets
22070	Amitriptyline Hydrochloride	10mg/5ml	Oral Solution
24145	Amitriptyline hydrochloride	25mg	Tablet
24147	Amitriptyline hydrochloride	25mg	Tablet
24152	Amitriptyline hydrochloride	10mg	Tablet
33090	Amitriptyline hydrochloride	10mg	Tablet
33624	Amitriptyline hydrochloride	50mg	Tablet
34224	Amitriptyline hydrochloride	5mg/1ml	Oral solution
34274	Amitriptyline hydrochloride	50mg	Tablet
34782	Amitriptyline hydrochloride	25mg	Tablet
38827	Amitriptyline hydrochloride/Perphenazine	10mg+2mg	Tablet
3194	Clomipramine hydrochloride	10mg	Capsule
3657	Clomipramine hydrochloride	25mg	Capsule
3670	Clomipramine hydrochloride	25mg	Capsule
3925	Clomipramine hydrochloride	50mg	Capsule
7515	Clomipramine hydrochloride	10mg	Capsule
7693	Clomipramine hydrochloride	50mg	Capsule
8661	Clomipramine hydrochloride	75mg	Capsule

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antidepressants			
Product code	**Drug**	**Strength**	**Formulation**
74	Dosulepin hydrochloride	75mg	Tablet
84	Dosulepin hydrochloride	25mg	Capsule
1169	Dosulepin hydrochloride	25mg	Capsule
1940	Dosulepin hydrochloride	25mg	Capsule
2320	Dosulepin hydrochloride	75mg	Tablet
6054	Dosulepin Hydrochloride	25mg/5ml	Oral Solution Sugar-free
10948	Dosulepin Hydrochloride	75mg/5ml	Oral Solution Sugar-free
15632	Dosulepin hydrochloride	75mg	Tablet
19186	Dosulepin hydrochloride	75mg	Tablet
21819	Dosulepin hydrochloride	75mg	Tablet
21820	Dosulepin hydrochloride	25mg	Capsule
23426	Dosulepin hydrochloride	25mg	Capsule
31824	Dosulepin hydrochloride	25mg	Capsule
31826	Dosulepin hydrochloride	75mg	Tablet
32121	Dosulepin hydrochloride	75mg	Tablet
34641	Dosulepin hydrochloride	25mg	Capsule
3554	Doxepin hydrochloride	25mg	Capsule
3842	Doxepin hydrochloride	10mg	Capsule
5073	Doxepin hydrochloride	50mg	Capsule
7059	Doxepin hydrochloride	75mg	Capsule
10413	Doxepin hydrochloride	10mg	Capsule
12125	Doxepin hydrochloride	50mg	Capsule
12129	Doxepin hydrochloride	25mg	Capsule
1310	Imipramine hydrochloride	10mg	Tablet
1809	Imipramine hydrochloride	25mg	Tablet
4404	Imipramine hydrochloride	5mg/1ml	Oral solution
7910	Imipramine hydrochloride	25mg	Tablet
8055	Imipramine hydrochloride	5mg/1ml	Oral solution
42247	Imipramine hydrochloride	5mg/1ml	Oral solution
114	Lofepramine hydrochloride	70mg	Tablet
2093	Lofepramine hydrochloride	70mg	Tablet
4218	Lofepramine hydrochloride	14mg/1ml	Oral suspension
34578	Lofepramine hydrochloride	70mg	Tablet
3183	Nortriptyline hydrochloride	10mg	Tablet
3903	Nortriptyline hydrochloride	25mg	Tablet
8640	Nortriptyline hydrochloride	25mg	Tablet
2039	Trimipramine maleate	25mg	Tablet
2531	Trimipramine maleate	50mg	Capsule
2532	Trimipramine maleate	25mg	Tablet
3196	Trimipramine maleate	50mg	Capsule

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antidepressants			
Product code	**Drug**	**Strength**	**Formulation**
4310	Trimipramine maleate	10mg	Tablet
67	Citalopram hydrobromide	20mg	Tablet
476	Citalopram hydrobromide	10mg	Tablet
513	Citalopram hydrochloride	40mg/1ml	Oral drops
815	Citalopram hydrochloride	40mg/1ml	Oral drops
1712	Citalopram hydrobromide	20mg	Tablet
2408	Citalopram hydrobromide	40mg	Tablet
3861	Citalopram hydrobromide	10mg	Tablet
4770	Citalopram hydrobromide	40mg	Tablet
26016	Citalopram hydrobromide	20mg	Tablet
34415	Citalopram hydrobromide	20mg	Tablet
34499	Citalopram hydrobromide	10mg	Tablet
603	Escitalopram oxalate	10mg	Tablet
648	Escitalopram oxalate	10mg	Tablet
785	Escitalopram oxalate	5mg	Tablet
6218	Escitalopram oxalate	20mg	Tablet
6360	Escitalopram oxalate	20mg	Tablet
6405	Escitalopram oxalate	5mg	Tablet
20152	Escitalopram oxalate	10mg/1ml	Oral drops
26056	Escitalopram oxalate	10mg/1ml	Oral drops
22	Fluoxetine hydrochloride	20mg	Capsule
252	Fluoxetine hydrochloride	4mg/1ml	Oral solution
418	Fluoxetine hydrochloride	20mg	Capsule
2548	Fluoxetine hydrochloride	4mg/1ml	Oral solution
4075	Fluoxetine hydrochloride	60mg	Capsule
14740	Fluoxetine hydrochloride	20mg	Capsule
36893	Fluoxetine hydrochloride	4mg/1ml	Oral solution
2290	Fluvoxamine maleate	100mg	Tablet
2880	Fluvoxamine maleate	50mg	Tablet
2897	Fluvoxamine maleate	50mg	Tablet
50	Paroxetine hydrochloride	20mg	Tablet
527	Paroxetine hydrochloride	2mg/1ml	Oral suspension
841	Paroxetine hydrochloride	20mg	Tablet
1397	Paroxetine hydrochloride	30mg	Tablet
1575	Paroxetine hydrochloride	30mg	Tablet
3601	Paroxetine hydrochloride	2mg/1ml	Oral suspension
34351	Paroxetine hydrochloride	20mg	Tablet
35021	Paroxetine hydrochloride	10mg	Tablet
35112	Paroxetine hydrochloride	10mg	Tablet
488	Sertraline hydrochloride	50mg	Tablet

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antidepressants			
Product code	**Drug**	**Strength**	**Formulation**
727	Sertraline hydrochloride	100mg	Tablet
1612	Sertraline hydrochloride	50mg	Tablet
4352	Sertraline hydrochloride	100mg	Tablet
7328	Sertraline hydrochloride	10mg/1ml	Oral suspension
3349	Phenelzine sulphate	15mg	Tablet
4321	Phenelzine sulphate	15mg	Tablet
12207	Isocarboxazid	10mg	Tablet
3783	Tranylcypromine sulphate	10mg	Tablet
3083	Mianserin hydrochloride	10mg	Tablet
4329	Mianserin hydrochloride	20mg	Tablet
6255	Mianserin hydrochloride	30mg	Tablet
2883	Moclobemide	150mg	Tablet
5187	Moclobemide	300mg	Tablet
40295	Agomelatine	25mg	Tablet
40494	Agomelatine	25mg	Tablet
6895	Duloxetine hydrochloride	60mg	Gastro-resistant capsule
7122	Duloxetine hydrochloride	30mg	Gastro-resistant capsule
13151	Duloxetine hydrochloride	30mg	Gastro-resistant capsule
14849	Duloxetine hydrochloride	60mg	Gastro-resistant capsule
51383	Duloxetine hydrochloride	60mg	Gastro-resistant capsule
2275	Flupentixol dihydrochloride	500microgram	Tablet
3953	Flupentixol dihydrochloride	500microgram	Tablet
59593	Flupentixol dihydrochloride	500microgram	Tablet
742	Mirtazapine	30mg	Tablet
4726	Mirtazapine	30mg	Tablet
6421	Mirtazapine	15mg	Orodispersible tablet
6481	Mirtazapine	45mg	Orodispersible tablet
6488	Mirtazapine	30mg	Orodispersible tablet
6795	Mirtazapine	15mg	Tablet
6846	Mirtazapine	15mg	Orodispersible tablet
6854	Mirtazapine	45mg	Tablet
10083	Mirtazapine	30mg	Orodispersible tablet
15268	Mirtazapine	45mg	Orodispersible tablet
16154	Mirtazapine	15mg/1ml	Oral solution
33337	Mirtazapine	45mg	Tablet
40160	Mirtazapine	30mg	Tablet
43234	Mirtazapine	45mg	Orodispersible tablet
43235	Mirtazapine	45mg	Orodispersible tablet
43236	Mirtazapine	45mg	Orodispersible tablet
43237	Mirtazapine	15mg	Orodispersible tablet

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antidepressants			
Product code	**Drug**	**Strength**	**Formulation**
43239	Mirtazapine	15mg	Tablet
43241	Mirtazapine	15mg	Orodispersible tablet
43242	Mirtazapine	15mg	Tablet
43246	Mirtazapine	15mg	Orodispersible tablet
43247	Mirtazapine	45mg	Orodispersible tablet
43248	Mirtazapine	15mg	Orodispersible tablet
43250	Mirtazapine	30mg	Orodispersible tablet
43253	Mirtazapine	15mg	Orodispersible tablet
43256	Mirtazapine	45mg	Orodispersible tablet
43257	Mirtazapine	15mg	Tablet
46668	Mirtazapine	15mg	Tablet
47945	Mirtazapine	30mg	Tablet
47966	Mirtazapine	15mg/1ml	Oral solution
48185	Mirtazapine	30mg	Orodispersible tablet
50892	Mirtazapine	15mg	Orodispersible tablet
53321	Mirtazapine	15mg/1ml	Oral solution
53543	Mirtazapine	30mg	Orodispersible tablet
53648	Mirtazapine	30mg	Orodispersible tablet
53699	Mirtazapine	15mg	Tablet
54342	Mirtazapine	15mg	Tablet
54644	Mirtazapine	15mg	Tablet
54792	Mirtazapine	30mg	Tablet
55482	Mirtazapine	15mg	Orodispersible tablet
56209	Mirtazapine	30mg	Tablet
58291	Mirtazapine	15mg	Orodispersible tablet
58625	Mirtazapine	45mg	Tablet
59694	Mirtazapine	30mg	Orodispersible tablet
59953	Mirtazapine	15mg	Tablet
59954	Mirtazapine	45mg	Tablet
60370	Mirtazapine	15mg	Orodispersible tablet
60538	Mirtazapine	30mg	Tablet
61547	Mirtazapine	15mg/1ml	Oral solution
61856	Mirtazapine	15mg	Orodispersible tablet
2356	Reboxetine mesilate	4mg	Tablet
15163	Reboxetine mesilate	4mg	Tablet
301	Venlafaxine hydrochloride	37.5mg	Tablet
470	Venlafaxine hydrochloride	75mg	Modified-release capsule
623	Venlafaxine hydrochloride	37.5mg	Tablet
1222	Venlafaxine hydrochloride	75mg	Tablet
1474	Venlafaxine hydrochloride	75mg	Modified-release capsule

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antidepressants			
Product code	**Drug**	**Strength**	**Formulation**
2617	Venlafaxine hydrochloride	50mg	Tablet
2654	Venlafaxine hydrochloride	150mg	Modified-release capsule
5710	Venlafaxine hydrochloride	150mg	Modified-release capsule
6274	Venlafaxine hydrochloride	50mg	Tablet
9182	Venlafaxine hydrochloride	75mg	Tablet
13237	Venlafaxine hydrochloride	7.5mg/1ml	Oral suspension
39359	Venlafaxine Hydrochloride	75mg	Modified Release Tablet
39360	Venlafaxine Hydrochloride	150mg	Modified Release Tablet
39770	Venlafaxine hydrochloride	75mg	Modified-release capsule
39809	Venlafaxine hydrochloride	150mg	Modified-release capsule
40048	Venlafaxine hydrochloride	75mg	Modified-release tablet
40049	Venlafaxine hydrochloride	150mg	Modified-release tablet
40054	Venlafaxine Hydrochloride	225mg	Modified Release Tablet
40059	Venlafaxine Hydrochloride	75mg	Modified Release Tablet
40062	Venlafaxine Hydrochloride	150mg	Modified Release Tablet
40092	Venlafaxine hydrochloride	150mg	Modified-release capsule
40277	Venlafaxine hydrochloride	75mg	Modified-release capsule
40407	Venlafaxine Hydrochloride	225mg	Modified Release Tablet
40514	Venlafaxine hydrochloride	150mg	Modified-release capsule
40515	Venlafaxine hydrochloride	75mg	Modified-release capsule
40517	Venlafaxine hydrochloride	150mg	Modified-release capsule
40764	Venlafaxine hydrochloride	37.5mg	Tablet
40815	Venlafaxine hydrochloride	75mg	Modified-release capsule
40817	Venlafaxine hydrochloride	150mg	Modified-release capsule
40917	Venlafaxine hydrochloride	75mg	Tablet
41033	Venlafaxine hydrochloride	75mg	Modified-release capsule
41299	Venlafaxine hydrochloride	75mg	Modified-release capsule
41314	Venlafaxine hydrochloride	150mg	Modified-release capsule
42600	Venlafaxine hydrochloride	75mg	Modified-release capsule
43203	Venlafaxine hydrochloride	75mg	Modified-release capsule
43334	Venlafaxine hydrochloride	150mg	Modified-release capsule
43673	Venlafaxine hydrochloride	150mg	Modified-release capsule
43968	Venlafaxine hydrochloride	75mg	Modified-release capsule
44936	Venlafaxine hydrochloride	150mg	Modified-release capsule
44937	Venlafaxine hydrochloride	75mg	Modified-release capsule
45664	Venlafaxine hydrochloride	150mg	Modified-release capsule
45806	Venlafaxine Hydrochloride	37.5mg	Modified Release Tablet
45818	Venlafaxine Hydrochloride	37.5mg	Modified Release Tablet
45959	Venlafaxine hydrochloride	75mg	Modified-release capsule
48199	Venlafaxine hydrochloride	75mg	Modified-release capsule

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antidepressants			
Product code	**Drug**	**Strength**	**Formulation**
49511	Venlafaxine hydrochloride	75mg	Modified-release capsule
50081	Venlafaxine hydrochloride	150mg	Modified-release capsule
50934	Venlafaxine hydrochloride	30mg/1ml	Oral solution
51280	Venlafaxine hydrochloride	150mg	Modified-release capsule
51361	Venlafaxine hydrochloride	37.5mg	Tablet
52074	Venlafaxine hydrochloride	75mg	Modified-release capsule
52516	Venlafaxine hydrochloride	150mg	Modified-release capsule
52716	Venlafaxine hydrochloride	75mg	Modified-release capsule
53326	Venlafaxine hydrochloride	15mg/1ml	Oral solution
55424	Venlafaxine Hydrochloride		
55501	Venlafaxine hydrochloride	150mg	Modified-release capsule
56457	Venlafaxine hydrochloride	75mg	Tablet
56662	Venlafaxine hydrochloride	37.5mg	Tablet
57751	Venlafaxine hydrochloride	150mg	Modified-release capsule
59563	Venlafaxine hydrochloride	75mg	Modified-release capsule
59923	Venlafaxine hydrochloride	37.5mg	Tablet
60449	Venlafaxine hydrochloride	75mg	Tablet
60549	Venlafaxine hydrochloride	150mg	Modified-release capsule
60895	Venlafaxine hydrochloride	37.5mg	Tablet
61236	Venlafaxine hydrochloride	150mg	Modified-release capsule
9696	Alprazolam	250mcg	Tablet
10802	Alprazolam	250mcg	Tablet
11486	Alprazolam	500mcg	Tablet
12598	Alprazolam	500mcg	Tablet
Benzodiazepines			
Product code	**Drug**	**Strength**	**Formulation**
1463	Chlordiazepoxide hydrochloride	10mg	Capsule
2122	Chlordiazepoxide hydrochloride	5mg	Capsule
3147	Chlordiazepoxide Hydrochloride	10mg	Tablets
4543	Chlordiazepoxide Hydrochloride	5mg	Tablets
5294	Chlordiazepoxide hydrochloride	10mg	Tablet
6025	Chlordiazepoxide hydrochloride	5mg	Tablet
6516	Chlordiazepoxide Hydrochloride	25mg	Tablets
18125	Chlordiazepoxide hydrochloride	5mg	Capsule
46	Diazepam	2mg	Tablet
47	Diazepam	5mg	Tablet
1400	Diazepam	10mg	Tablet
2352	Diazepam	400mcg/1ml	Oral solution
10274	Diazepam	400mcg/1ml	Oral solution
9065	Diazepam	1mg/1ml	Oral solution

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Benzodiazepines			
Product code	**Drug**	**Strength**	**Formulation**
9430	Diazepam	2.5mg/5ml	Suspension
41607	Diazepam	10mg	Tablet
12849	Diazepam	10mg/5ml	Suspension
29945	Diazepam	2mg	Tablet
9045	Diazepam	1mg/5ml	Suspension
32296	Diazepam	5mg	Tablet
3105	Flurazepam hydrochloride	30mg	Capsule
3950	Flurazepam hydrochloride	15mg	Capsule
3956	Flurazepam hydrochloride	15mg	Capsule
7566	Flurazepam hydrochloride	30mg	Capsule
5150	Loprazolam mesilate	1mg	Tablet
1088	Lorazepam	1mg	Tablet
13279	Lorazepam	100mcg/1ml	Oral suspension
37566	Lorazepam	200mcg/1ml	Oral suspension
2091	Lorazepam	2.5mg	Tablet
39284	Lorazepam	1mg	Tablet
37745	Lorazepam	200mcg/1ml	Oral solution
3354	Lormetazepam	1mg	Tablet
3687	Lormetazepam	500mcg	Tablet
3357	Lormetazepam	1mg	Capsule
35	Nitrazepam	5mg	Tablet
7924	Nitrazepam	500mcg/1ml	Oral suspension
7786	Nitrazepam	5mg	Tablet
19450	Nitrazepam	5mg	Tablet
41385	Nitrazepam	5mg	Tablet
9814	Nitrazepam	1mg/1ml	Oral suspension
34555	Nitrazepam	5mg	Tablet
4566	Oxazepam	10mg	Tablet
4141	Oxazepam	15mg	Tablet
41531	Oxazepam	10mg	Tablet
46946	Oxazepam	15mg	Tablet
20	Temazepam	10mg	Tablet
780	Temazepam	2mg/1ml	Oral solution
1729	Temazepam	20mg	Tablet
34331	Temazepam	10mg	Tablet
30779	Temazepam	20mg	Tablet
41718	Temazepam	10mg	Capsule
34406	Temazepam	10mg	Tablet

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Non-benzodiazepines			
Product code	**Drug**	**Strength**	**Formulation**
14415	Amobarbital sodium	60mg	Capsule
13471	Amobarbital sodium	200mg	Capsule
8548	Amobarbital sodium	200mg	Capsule
28146	Amobarbital sodium	60mg	Capsule
221	Amobarbital sodium/Secobarbital sodium	50mg +50mg	Capsule
12264	Secobarbital sodium	100mg	Capsule
12539	Secobarbital sodium	50mg	Capsule
14613	Secobarbital sodium	100mg	Capsule
26775	Secobarbital sodium	50mg	Capsule
13447	Butobarbital	100mg	Tablet
8624	Butobarbital	100mg	Tablet
3574	Buspirone hydrochloride	5mg	Tablet
2394	Buspirone hydrochloride	5mg	Tablet
5385	Buspirone hydrochloride	10mg	Tablet
9008	Buspirone hydrochloride	10mg	Tablet
3580	Chloral hydrate	28.66mg/1ml	Oral solution
3928	Chloral hydrate	28.66mg/1ml	Oral solution
4017	Chloral Hydrate	500mg/5ml	Syrup
4018	Chloral Hydrate	1g/5ml	Syrup
12898	Chloral hydrate/Syrup	100mg/1ml +200microlitre/1ml	Oral solution
563	Clomethiazole	192mg	Capsule
3491	Clomethiazole	192mg	Capsule
2535	Clomethiazole edisilate	50mg/1ml	Oral solution
1546	Hydroxyzine hydrochloride	25mg	Tablet
40472	Hydroxyzine hydrochloride	25mg	Tablet
40510	Hydroxyzine hydrochloride	10mg	Tablet
1913	Hydroxyzine hydrochloride	10mg	Tablet
878	Hydroxyzine hydrochloride	10mg	Tablet
683	Hydroxyzine hydrochloride	25mg	Tablet
10068	Melatonin	1mg	Capsule
38208	Melatonin	2mg	Modified-release tablet
38265	Melatonin	2mg	Modified-release tablet
14145	Melatonin	3mg	Capsule
7099	Melatonin	2mg	Capsule
35224	Melatonin	5mg	Capsule
13023	Melatonin	2.5mg	Capsule

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Non-benzodiazepines			
Product code	**Drug**	**Strength**	**Formulation**
26391	Melatonin	10mg	Capsule
16993	Melatonin	3mg	Modified-release capsule
2828	Meprobamate	400mg	Tablet
5916	Zaleplon	5mg	Capsule
5352	Zaleplon	10mg	Capsule
9598	Zaleplon	5mg	Capsule
5306	Zaleplon	10mg	Capsule
3126	Zolpidem tartrate	5mg	Tablet
3741	Zolpidem tartrate	10mg	Tablet
5459	Zolpidem tartrate	10mg	Tablet
2017	Zolpidem tartrate	5mg	Tablet
30981	Zolpidem tartrate	10mg	Tablet
66	Zopiclone	7.5mg	Tablet
3320	Zopiclone	7.5mg	Tablet
34874	Zopiclone	7.5mg	Tablet
721	Zopiclone	3.75mg	Tablet
4187	Zopiclone	3.75mg	Tablet
24135	Zopiclone	7.5mg	Tablet
15852	Zopiclone	7.5mg	Tablet
14365	Zopiclone	750mcg/1ml	Oral suspension
29219	Zopiclone	3.75mg	Tablet
Antipsychotics			
Product code	**Drug**	**Strength**	**Formulation**
4876	Amisulpride	50mg	Tablet
5071	Amisulpride	200mg	Tablet
5927	Amisulpride	400mg	Tablet
6482	Amisulpride	100mg/1ml	Oral solution
6524	Amisulpride	100mg	Tablet
11938	Amisulpride	5mg/1ml	Oral suspension
16768	Amisulpride	50mg	Tablet
1453	Amitriptyline hydrochloride/Perphenazine	10mg + 2mg	Tablet
16561	Aripiprazole	30mg	Tablet
14344	Aripiprazole	5mg	Tablet

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antipsychotics			
Product code	**Drug**	**Strength**	**Formulation**
14858	Aripiprazole	15mg	Tablet
6561	Aripiprazole	10mg	Tablet
16575	Aripiprazole	1mg/1ml	Oral solution
18132	Aripiprazole	5mg	Tablet
6573	Aripiprazole	15mg	Tablet
32076	Aripiprazole	10mg	Orodispersible tablet
24358	Aripiprazole	10mg	Tablet
38080	Aripiprazole	1mg/1ml	Oral solution
2540	Benperidol	250mcg	Tablet
588	Chlorpromazine hydrochloride	25mg	Tablet
3348	Chlorpromazine hydrochloride	50mg	Tablet
2154	Chlorpromazine hydrochloride	100mg	Tablet
3952	Chlorpromazine hydrochloride	5mg/1ml	Oral solution
8771	Chlorpromazine hydrochloride	10mg	Tablet
2814	Chlorpromazine hydrochloride	25mg	Tablet
8519	Chlorpromazine hydrochloride	20mg/1ml	Oral solution
10434	Chlorpromazine hydrochloride	5mg/1ml	Oral solution
9190	Chlorpromazine hydrochloride	5mg/1ml	Oral solution
3772	Chlorpromazine hydrochloride	50mg	Tablet
4434	Chlorpromazine hydrochloride	10mg/1ml	Oral solution
42242	Clozapine	50mg/ml	Oral Suspension
45444	Clozapine	50mg/1ml	Oral suspension
8047	Clozapine	100mg	Tablet
40587	Clozapine	200mg	Tablets
17958	Clozapine	25mg	Tablet
2275	Flupentixol dihydrochloride	500microgram	Tablet
5707	Flupentixol dihydrochloride	3mg	Tablet
5712	Flupentixol dihydrochloride	3mg	Tablet
2419	Haloperidol	500mcg	Capsule
329	Haloperidol	1.5mg	Tablet
5192	Haloperidol	1mg/5ml	Oral Solution
9975	Haloperidol	1mg/ml	Oral Solution
3233	Haloperidol	2mg/ml	Liquid
2621	Haloperidol	5mg	Tablet
13105	Haloperidol	2mg/ml	Oral Solution
2620	Haloperidol	1mg/ml	Oral Solution
8979	Haloperidol	1.5mg	Tablet
12387	Haloperidol	20mg	Tablet
5545	Haloperidol	500mcg	Capsule

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antipsychotics			
Product code	**Drug**	**Strength**	**Formulation**
32838	Haloperidol	1.5mg	Tablet
22660	Haloperidol	5mg	Tablet
36771	Haloperidol	250mcg/5ml	Oral Suspension
8153	Haloperidol	2mg/1ml	Oral solution
12921	Haloperidol	2mg/1ml	Oral solution
475	Haloperidol	10mg	Tablet
5014	Levomepromazine maleate	25mg	Tablet
4232	Levomepromazine maleate	25mg	Tablet
7390	Levomepromazine maleate	6mg	Tablet
40782	Levomepromazine Maleate	6mg	Tablet
28231	Levomepromazine maleate	6mg	Tablet
2656	Olanzapine	2.5mg	Tablet
3281	Olanzapine	5mg	Tablet
5653	Olanzapine	7.5mg	Tablet
6412	Olanzapine	5mg	Orodispersible Tablet
1249	Olanzapine	10mg	Tablet
6850	Olanzapine	15mg	Tablet
6023	Olanzapine	10mg	Orodispersible Tablet
18024	Olanzapine	5mg	Tablet
29540	Olanzapine	20mg	Tablet
16103	Olanzapine	20mg	Orodispersible Tablet
6838	Olanzapine	15mg	Orodispersible Tablet
18453	Olanzapine	2.5mg	Tablet
14717	Olanzapine	5mg	Oral lyophilisate
37501	Paliperidone	9mg	Modified Release Tablet
37717	Paliperidone	3mg	Modified-release tablet
36954	Paliperidone	6mg	Modified-release tablet
7834	Pericyazine	2.5mg	Tablet
13902	Pericyazine	2mg/1ml	Oral solution
8032	Pericyazine	10mg	Tablet
12195	Pericyazine	2mg/1ml	Oral solution
7833	Pericyazine	2.5mg	Tablet
7919	Perphenazine	4mg	Tablet
609	Perphenazine	2mg	Tablet
2157	Perphenazine	4mg	Tablet
840	Perphenazine	2mg	Tablet
5821	Pimozide	4mg	Tablet
2489	Pimozide	2mg	Tablet
8637	Pimozide	10mg	Tablets

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antipsychotics			
Product code	**Drug**	**Strength**	**Formulation**
85	Prochlorperazine maleate	5mg	Tablet
500	Prochlorperazine maleate	3mg	Buccal tablet
39887	Prochlorperazine maleate	5mg	Tablet
512	Prochlorperazine maleate	5mg	Tablet
227	Prochlorperazine maleate	5mg	Suppository
1234	Prochlorperazine maleate	25mg	Suppository
1990	Prochlorperazine maleate	25mg	Suppository
32551	Prochlorperazine maleate	5mg	Tablet
1434	Prochlorperazine maleate	5mg	Suppository
13607	Prochlorperazine maleate	5mg	Tablet
32876	Prochlorperazine maleate	5mg	Tablet
6036	Prochlorperazine mesilate	1mg/1ml	Oral solution
40001	Prochlorperazine mesilate	1mg/1ml	Oral solution
7593	Prochlorperazine mesilate	1mg/1ml	Oral solution
2972	Promazine hydrochloride	25mg	Tablet
10780	Promazine Hydrochloride	50mg/5ml	Suspension
6443	Promazine hydrochloride	5mg/1ml	Oral solution
3228	Promazine hydrochloride	50mg	Tablet
17634	Promazine hydrochloride	10mg/1ml	Oral solution
14610	Promazine Hydrochloride	50mg/5ml	Syrup Sugar-free
5283	Quetiapine fumarate	25mg	Tablet
9794	Quetiapine fumarate	200mg	Tablet
5040	Quetiapine fumarate	150mg	Tablet
38885	Quetiapine Fumarate	50mg	Modified Release Tablet
7039	Quetiapine fumarate	300mg	Tablet
5039	Quetiapine fumarate	100mg	Tablet
14859	Quetiapine fumarate	25mg	Tablet
38906	Quetiapine fumarate	300mg	Modified-release tablet
38912	Quetiapine fumarate	200mg	Modified-release tablet
38840	Quetiapine fumarate	400mg	Modified-release tablet
38937	Quetiapine fumarate	300mg	Modified-release tablet
6864	Quetiapine fumarate	200mg	Tablet
38914	Quetiapine fumarate	200mg	Modified-release tablet
40779	Quetiapine fumarate	20mg/1ml	Oral solution
40932	Quetiapine fumarate	20mg/1ml	Oral suspension
39237	Quetiapine fumarate	400mg	Modified-release tablet
667	Risperidone	500mcg	Tablet
1320	Risperidone	1mg	Tablet
5219	Risperidone	3mg	Tablet

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antipsychotics			
Product code	**Drug**	**Strength**	**Formulation**
2787	Risperidone	4mg	Tablet
4820	Risperidone	1mg	Tablet
631	Risperidone	500mcg	Tablet
1321	Risperidone	2mg	Tablet
6373	Risperidone	1mg	Orodispersible tablet
11821	Risperidone	500mcg	Orodispersible tablet
302	Risperidone	1mg/1ml	Oral solution
16986	Risperidone	1mg	Orodispersible tablet
5262	Risperidone	1mg/1ml	Oral solution
7382	Risperidone	500mcg	Orodispersible tablet
9475	Risperidone	4mg	Tablet
9659	Risperidone	2mg	Tablet
16006	Risperidone	2mg	Orodispersible tablet
11828	Risperidone	2mg	Orodispersible tablet
35953	Risperidone	4mg	Orodispersible tablet
9340	Risperidone	3mg	Tablet
11799	Risperidone	6mg	Tablet
10666	Sulpiride	200mg	Tablet
2135	Sulpiride	200mg	Tablet
8903	Sulpiride	40mg/1ml	Oral solution
9247	Sulpiride	400mg	Tablet
1857	Trifluoperazine hydrochloride	1mg	Tablet
13145	Trifluoperazine hydrochloride	200mcg/1ml	Oral solution
1245	Trifluoperazine hydrochloride	5mg	Tablet
1318	Trifluoperazine hydrochloride	1mg	Tablet
8985	Trifluoperazine hydrochloride	200mcg/1ml	Oral solution
1316	Trifluoperazine hydrochloride	5mg	Tablet
11531	Trifluoperazine hydrochloride	1mg/1ml	Oral solution
12707	Zuclopenthixol dihydrochloride	2mg	Tablet
13368	Zuclopenthixol dihydrochloride	2mg	Tablet
9686	Zuclopenthixol dihydrochloride	10mg	Tablet
1319	Zuclopenthixol dihydrochloride	10mg	Tablet
13600	Zuclopenthixol dihydrochloride	25mg	Tablet
Antiepileptic's			
Product code	**Drug**	**Strength**	**Formulation**
1158	Carbamazepine	200mg	Tablet
432	Carbamazepine	100mg	Tablet
2388	Carbamazepine	200mg	Modified-release tablet

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antiepileptic's			
Product code	**Drug**	**Strength**	**Formulation**
596	Carbamazepine	20mg/1ml	Oral suspension
5977	Carbamazepine	100mg	Tablet
2085	Carbamazepine	200mg	Tablet
3569	Carbamazepine	400mg	Modified-release tablet
652	Carbamazepine	400mg	Tablet
6594	Carbamazepine	20mg/1ml	Oral suspension
5076	Carbamazepine	400mg	Tablet
17564	Carbamazepine	100mg	Chewable tablet
5449	Carbamazepine	100mg	Chewable tablet
7538	Carbamazepine	200mg	Chewable tablet
41137	Carbamazepine	200mg	Chewable tablet
660	Gabapentin	100mg	Capsule
4781	Gabapentin	400mg	Capsule
5221	Gabapentin	600mg	Tablet
1584	Gabapentin	300mg	Capsule
10007	Gabapentin	100mg	Capsule
7011	Gabapentin	300mg	Capsule
5874	Gabapentin	600mg	Tablet
3845	Gabapentin	80mg/1ml	Oral suspension
7023	Gabapentin	800mg	Tablet
35024	Gabapentin	400mg	Capsule
6858	Gabapentin	300mg	Capsule
36318	Gabapentin	50mg/1ml	Oral suspension
15851	Gabapentin	50mg/1ml	Oral solution
6936	Pregabalin	50mg	Capsule
790	Pregabalin	25mg	Capsule
6999	Pregabalin	100mg	Capsule
819	Pregabalin	75mg	Capsule
6584	Pregabalin	75mg	Capsule
6949	Pregabalin	200mg	Capsule
16542	Pregabalin	25mg	Capsule
6631	Pregabalin	150mg	Capsule
37801	Pregabalin	225mg	Capsule
7005	Pregabalin	300mg	Capsule
7209	Pregabalin	50mg	Capsule
10189	Pregabalin	300mg	Capsule
6820	Pregabalin	150mg	Capsule
11696	Pregabalin	200mg	Capsule
4175	Pregabalin	100mg	Capsule

Antiepileptic product codes that resulted in matchings are only presented

(Continued) Appendix 16 Product codes of antidepressants, benzodiazepines, non-benzodiazepines, antipsychotics and antiepileptics

Antiepileptic's			
Product code	**Drug**	**Strength**	**Formulation**
39279	Sodium Valproate	500mg	Modified Release granule
584	Sodium valproate	200mg	Gastro-resistant tablet
6711	Sodium valproate	300mg	Modified-release tablet
3107	Sodium valproate	500mg	Modified-release tablet
3350	Sodium valproate	500mg	Gastro-resistant tablet
3733	Sodium valproate	300mg	Modified-release tablet
2822	Sodium valproate	500mg	Gastro-resistant tablet
38949	Sodium valproate	500mg	Gastro-resistant tablet
3734	Sodium valproate	200mg	Modified-release tablet
38939	Sodium valproate	200mg	Gastro-resistant tablet
4913	Sodium valproate	150mg	Modified-release capsule
4066	Sodium valproate	100mg	Tablet
4502	Sodium valproate	200mg	Gastro-resistant tablet
2082	Sodium Valproate	300mg	Modified Release Tablet
6068	Sodium valproate	500mg	Modified-release tablet
10263	Sodium valproate	100mg	Tablet
7394	Sodium valproate	300mg	Modified-release capsule
5830	Sodium valproate	200mg	Modified-release tablet
107	Sodium Valproate	1000mg	Modified Release Granules
11237	Topiramate	25mg	Tablet
7073	Topiramate	50mg	Tablet
6552	Topiramate	100mg	Tablet
16509	Topiramate	50mg	Tablet
13608	Topiramate	25mg	Capsule
16215	Topiramate	50mg	Capsule
6021	Topiramate	200mg	Tablet
7108	Topiramate	25mg	Tablet
20640	Topiramate	15mg	Capsule
11075	Topiramate	100mg	Tablet

Antiepileptic product codes that resulted in matchings are only presented

Appendix 17 Missing NDD of co-prescribed psychoactive and "other" analgesic drugs

Drug	Total number of prescriptions	No of prescriptions with missing NDD (%)
Benzodiazepines	48,880	17,480 (35.76)
Non-benzodiazepines	200,332	27,412 (13.68)
Antidepressants	657,505	83,383 (12.68)
Antipsychotics	19,846	4,903 (24.71)
Anticonvulsants	297,758	63,085 (21.19)
NSAIDs	416,852	51,815 (12.43)
Paracetamol	445,795	78,586 (17.63)
Tramadol	256,263	83,685 (32.66)
Weak opioids	504,864	90,477 (17.92)

Results of NDD imputation diagnostics

	NDD data			
	Observed data (without imputation)		Imputed data	
Drug	**Mean**	**Median (IQR)**	**Mean**	**Median (IQR)**
Benzodiazepines	1.92 (1.64)	1 (1-3)	2.15 (1.98)	2 (1-3)
Non-benzodiazepines	1.26 (0.82)	1 (1-1)	1.27 (0.89)	1 (1-1)
Antidepressants	1.64 (4.29)	1 (1-2)	1.63 (4.14)	1 (1-2)
Antipsychotics	2.71 (2.63)	3 (2-3)	2.74 (2.68)	3 (2-3)
Anticonvulsants	4.25 (25.14)	3 (2-3)	4.33 (24.51)	3 (2-3)
NSAIDs	2.54 (10.59)	2 (2-3)	2.61 (10.20)	2 (2-3)
Paracetamol	7.61 (6.35)	7 (6-8)	7.94 (7.67)	6 (6-8)
Tramadol	4.67 (3.51)	5 (2-6)	4.98 (2.99)	6 (3-6)
Weak opioids	6.15 (2.38)	6 (6-6)	6.08 (2.38)	6 (6-6)

Appendix 18 Generalized estimating equation for longitudinal data analysis

Longitudinal collected data are increasingly common and often arise in practice, either in observational research or in experimental studies. A prime feature of any longitudinally examined data is that the repeat measurements of the same individual or over time are positively correlated. Such intra-individual data dependency violates the conditional independence requirements needed to apply multivariate regression modelling. If not managed appropriately this can lead to inaccuracy in parameter estimates of the regression model adopted for data analysis. Amongst the various approaches developed to manage longitudinal data's conditional dependence, the most widely used includes the generalized estimating equation models [226, 227].

The GEE is an extension of the generalized linear model, which generalizes the explicit independence of repeat observations for a subject without assuming normality of distributions to account for correlation [475]. The GEE is based on analysing the marginal clustered data as a function of covariates. The marginal effect which is the mean average rate of change (over time) is studied in relation to covariates, this means that the GEE output would estimate the magnitude of change in the average response for every unit change in a covariate across a sample study [476]. The advantages of using the GEE model to analyse correlated longitudinal data is that they can be used for outcome measures with different distributional forms (e.g. binary) and the produce accurate estimates of β-coefficients and standard errors [227].

Appendix 19 Pearson correlation analyses of variables used in GEE models

	Gender	Region	Age	Socioeconomic status	Smoking-status	Ankylosing spondylisis	Back pain	Unspecified arthirits
Gender	1							
Region	0	1						
Age	0.09*	0	1					
Socioeconomic status	0.01	-0.17*	-0.12*	1				
Smokingstatus	-0.07*	-0.01*	0.10*	-0.04*	1			
Ankylosing spondylisis	-0.02*	0	-0.03*	0	0	1		
Back pain	0.02*	-0.03*	-0.09*	0.02*	-0.01*	0.01*	1	
Unspecified arthirits	0.02*	-0.01*	0.01*	0	0	0	-0.01*	1
Pancreatitis	-0.02*	-0.01	-0.06*	0.01*	0	0	-0.02*	0
Rheumatioid arthritis	0.02*	0	-0.01*	0	0.01	0	-0.01*	0.06*
Shoulder pain	0	0	-0.02*	0.01*	-0.01*	0	-0.01*	0.02*
Abdominal pain	0.03*	-0.02*	-0.06*	0.01*	-0.01*	0	0	-0.01*
Cervical pain	0	0	-0.01*	-0.01	0	0	0	0
Thoracic/chest pain	-0.01*	-0.02*	0.01*	0.01*	0.01*	0.01*	0.06*	0
Gout	0	0	0.01*	0	0	0	0	0.08*
Pelvic pain	0.02*	0.01	-0.03*	0	0	0	0	0
Menstrual pain	0.01*	0	-0.02*	0.01*	0	0	0.01	0
Postoperative pain	-0.01*	-0.01*	-0.03*	0.01	0	0	-0.01*	0
Gallstone/Kidney stone	-0.01*	-0.01*	-0.03*	0	0	0	-0.01*	0
Cervical spondylisis	0	-0.01*	0	0	0.01*	0.01*	-0.01*	0.01*
Colitis	0	0	-0.02*	0	0	0	0	0
Complex regional syndrome	0	0	-0.01*	0	0.01	0	0	0
Crohns disease	0	-0.01*	-0.04*	0	0	0.02*	0	0
Facial pain	0	0	-0.02*	0	0	0	0	0

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Gender	Region	Age	Socioeconomic status	Smoking-status	Ankylosing spondylisis	Back pain	Unspecified arthirits
Fibromyalgia	0.04*	0	-0.06*	0.01	-0.01*	0	0	0
Headache	0.01*	0	-0.07*	0.01*	-0.01	0.01	0.02*	0
Lupus	0.01*	0	-0.02*	0	-0.01	0	0	0
Migraine	0.03*	-0.01*	-0.08*	0	-0.01*	0	0.02*	0
Neck pain	0.01*	0	-0.02*	0	0	0	-0.01*	0
Neuropathy	-0.01*	0	-0.02*	0	0	0	0	0
Sciatica	-0.01*	-0.01*	-0.11*	0	-0.01*	-0.01*	0.17*	-0.01*
Spinal pain	-0.01*	-0.01*	0.01	0	0	0	0.05*	0
Temporaomandibular joint pain	0.01*	0	-0.02*	0.01	-0.01	0	0	0.01*
Trigeminal neuralgia	0	0	0	-0.01*	0	0	-0.01*	-0.01*
Osteoarhtirits	0.04*	-0.03*	0.07*	0	0	0	-0.01*	0.05*
Psoriatric arthropathy	0	0	-0.02*	0.01	0	0.01*	-0.01*	0.03*
Phantom limb	-0.01*	0	0	0	0	0	-0.01*	0
Post herpetic neuralgia	0	0	0.03*	-0.01*	0.01*	0	-0.01*	0
Learning disability	-0.01*	0	-0.01*	0	0	0	0	0
Epilepsy	-0.01	-0.01*	-0.02*	0.01*	0	0	-0.01*	0
Mental illness	0	0.01	0	0.01*	0	0	-0.01*	0
Dementia	0.01*	-0.01	0.07*	-0.01*	0.01*	0	-0.02*	0
Obesity	0.01*	0.02*	-0.02*	0.01*	-0.01	0	0.01*	0.01*
Hyperthyroidism	0.03*	-0.01	0.02*	0	-0.01*	0	0	0.01*
Heart failure	-0.02*	-0.02*	0.10*	-0.01*	0.01*	0	-0.02*	0
Atrial fibrillation	-0.01*	-0.01*	0.07*	-0.01*	0.01*	0	-0.01*	0
Asthma	0.02*	-0.01*	-0.05*	0.02*	0	0	0.02*	0
Stroke	0	-0.01*	0.08*	-0.01*	0.01*	0	-0.03*	0

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Gender	Region	Age	Socioeconomic status	Smoking-status	Ankylosing spondylisis	Back pain	Unspecified arthirits
Osteoporosis	0.06*	-0.01*	0.08*	0	0	0	0.08*	0
Diabetes	-0.02*	-0.01*	0.01*	0.02*	0	0	0	0
Coronary heart disease	-0.03*	-0.02*	0.06*	0	0.02*	0	-0.01*	0.01*
Hypertension	0.01*	-0.01*	0.02*	0.01*	0	0	0.01*	0.01*
Chronic pulmonary disease	-0.03*	-0.02*	0.05*	0.03*	0.05*	0	0	0
Chronic kidney disease	0.01*	0.01*	0.10*	-0.01*	0.01*	0	0	0.01
Depression	0	0	-0.04*	0.01*	0	0.01*	0.02*	0.01*
Anxiety	0.01*	-0.02*	-0.04*	0.02*	0	0	0.03*	0

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Pancreatitis	Rheumatioid arthritis	Shoulder pain	Abdominal pain	Cervical pain	Thoracic/chest pain	Gout	Pelvic pain	Menstrual pain	Postoperative pain
Pancreatitis	1									
Rheumatioid arthritis	0	1								
Shoulder pain	0	0.01*	1							
Abdominal pain	0.09*	-0.01*	-0.01*	1						
Cervical pain	0	0	0.01*	0	1					
Thoracic/chest pain	0	0	0.02*	0.04*	0	1				
Gout	0	0	0	-0.01	0	0	1			
Pelvic pain	0	0	-0.01*	0.05*	0	0	0	1		
Menstrual pain	0	0	0.01	0.02*	0	0	0	0	1	
Postoperative pain	0	0	0	0.02*	0	0	0	0	0	1
Gallstone/Kidney stone	0	0	0	0.02*	0	0	0	0	0	0.01*
Cervical spondylisis	0	0	0.03*	0	0.02*	0	0	0	0	0
Colitis	0	0	0	0.03*	0	0	0	0	0	0.01
Complex regional syndrome	0	0	0	0	0	0	0	0	0	0
Crohns disease	0	0	0	0.04*	0	0	0	0	0	0
Facial pain	0	0	0	0	0	0.01*	0	0	0	0
Fibromyalgia	0	0	0	0	0	0.01*	0	0	0.01*	0
Headache	0	0	0.02*	0.02*	0	0.03	0	0.01	0.01	0
Lupus	0	0.01*	0	0	0	0	0	0	0	0

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Pancreatitis	Rheumatioid arthritis	Shoulder pain	Abdominal pain	Cervical pain	Thoracic/chest pain	Gout	Pelvic pain	Menstrual pain	Postoperative pain
Migraine	0	0	0	0.02*	0	0	0	0.01*	0.01*	0
Neck pain	-0.01	0	0.06*	-0.01*	0.03*	0.01*	0	0	0	0
Neuropathy	0	0.01*	0.01	0	0.02*	0	0	0	0	0
Sciatica	-0.01*	-0.01*	-0.01*	-0.03*	0	-0.01*	0	0	0	-0.01*
Spinal pain	0	0	-0.01*	-0.01*	0	0	0.01*	0.01*	0	0
Temporaomandibular joint pain	0	0.01*	0.01*	0	0	0	0	0	0	0
Trigeminal neuralgia	0	0	0	-0.01	0	0	0	0	0	0
Osteoarhtirits	-0.01*	0.01	0.03*	-0.02*	0	-0.01*	0	0	0	-0.01
Psoriatric arthropathy	0	0.01*	0.01*	0	0	0	0	0	0	0
Phantom limb	0	0	0	0	0	0	0	0	0	0.02*
Post herpetic neuralgia	0	0	0.01*	0	0	0.01*	0.01*	0	0	0
Learning disability	0	0	0	0	0	0	0	0	0	0
Epilepsy	0	0	0	0.01	0	0	0	0	0	0
Mental illness	0	0	0	0	0	0	0	0	0	0
Dementia	0	-0.01*	0	0	0	-0.01*	0	0	0	0
Obesity	0	0	0.01	0	0	0.01*	0.01*	0	0	0
Hyperthyroidism	0	0.01*	0	0	0	0	0	0	0.01*	0
Heart failure	0	0	0	0.01*	0	0.04*	0	0	0	0
Atrial fibrillation	0	0	-0.01	0	0	0.03*	0	0	0	0

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Pancreatitis	Rheumatioid arthritis	Shoulder pain	Abdominal pain	Cervical pain	Thoracic/chest pain	Gout	Pelvic pain	Menstrual pain	Postoperative pain
Asthma	0	0	0	0.01*	0	0.02*	0	0	0	0
Stroke	-0.01*	0	-0.01	-0.01*	0	0	0	-0.01*	0	0
Osteoporosis	-0.01*	0.01*	0	0	0	0.06*	0.01	0	0	0
Diabetes	0.02*	0.01*	0	0	0	0.01*	0	-0.01	0	0.01
Coronary heart disease	-0.01*	0.01	0	0	0	0.12*	0	-0.01*	0	0
Hypertension	0	0.01*	0	-0.01	0	0.01*	0.01	0	0	0
Chronic pulmonary disease	0	0	0	0	0	0.06*	0	-0.01*	0	0
Chronic kidney disease	-0.01*	0	0	-0.01	0.01	0.01*	0.01*	0	0	0
Depression	0	0.01*	0.01*	0.02*	0	0.01*	0.01*	0	0	0.01*
Anxiety	0.01*	0	0.01*	0.02*	0	0.02*	0	0.01	0	0.01*

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Gallstones	Cervical Spondylisis	Colitis	Complex regional syndrome	Crohns disease	Facial pain	Fibromyalgia	Headache	Lupus	Migraine	Neck pain
Gallstones	1										
Cervical spondylisis	0	1									
Colitis	0	0	1								
Complex regional syndrome	0	0	0	1							
Crohns disease	0	0	0.09*	0	1						
Facial pain	0	0	0	0	0.01*	1					
Fibromyalgia	0	0	0	0	0	0	1				
Headache	0	0.03*	0	0	0	0.03*	0.01*	1			
Lupus	0	0	0	0	0	0	0	0.01*	1		
Migraine	0	0	0.01*	0.01*	0.01*	0.02*	0.02*	0.10*	0	1	
Neck pain	0	0.10*	0	0	0	0.01*	0.01	0.04*	0.01*	0.01*	1
Neuropathy	0	0	0	0	0	0.02*	0	0	0	0.01*	0.01*
Sciatica	0	-0.01*	-0.01	0	0	-0.01*	-0.01*	0	0	0	-0.01*
Spinal pain	0	0	0	0	0	0	0	0	0	0	0
Temporaomandibular joint pain	0	0	0	0	0.01*	0.02*	0	0.02*	0	0	0.01*
Trigeminal Neuralgia	0	0	0	0	0	0.11*	0	0.02*	0	0.01*	0
Osteoarhtirits	-0.01	0.02*	-0.01	0	-0.01*	0	0	0	0	-0.01*	0.01*
Psoriatric arthropathy	0	0	0	0	0	0	0	0	0	0	0
Phantom limb	0	0	0	0	0	0	0	0	0	0	0
Post herpetic Neuralgia	0	0	0.01	0	0	0.01*	0	0	0	0	0

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.0$

(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Gallstone	Cervical Spondylisis	Colitis	Complex regional syndrome	Crohns disease	Facial pain	Fibromyalgia	Headache	Lupus	Migraine	Neck pain
Learning disability	0	0	0	0	0	0.01*	0	0	0	0	0
Epilepsy	0	0	0	0	0.01	0	0	0.02*	0.01*	0	0
Mental illness	0	0	0	0	0	0	0	0	0	0	0
Dementia	0	0	0	0	0	0	0	-0.01	0	-0.01	0
Obesity	0.01*	0	0	0	0	0	0	0	0	0	0.01*
Hyperthyroidism	0	0	0.01*	0	0	0	0	0	0.01*	0	0.01
Heart failure	0	0	0	0	0	0	-0.01*	-0.01*	0	-0.01*	-0.01*
Atrial fibrillation	0	0	0	0	0	0	-0.01*	0	0	0	0
Asthma	0	0	0	0.01*	0.01*	0	0.01*	0.02*	0	0.02*	0.01*
Stroke	0	-0.01	0	0	0	0	-0.01*	0.01*	0	0	0
Osteoporosis	0	0	0.01*	0.01	0	0	0	0	0	0	0.02*
Diabetes	0	0	0	0	0	0	0	0	0	0	0
Coronary heart disease	0	0.01*	0	0	0	0	0	0	0	-0.01*	0.01
Hypertension	0	0.01	0	0.01	0	0	0	0.02*	0	0.01*	0
Chronic pulmonary disease	0	0	0	0	-0.01*	0	-0.01	0	0	-0.01*	0
Chronic kidney disease	0	0	0	0	0	0	-0.01*	0	0	-0.01	0
Depression	0	0.01	0	0	0	0	0.01*	0.02*	0.01*	0.01*	0
Anxiety	0.01*	0.01*	0	0	0	0	0.02*	0.03*	0.01*	0.02*	0.01*

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Neuropathy	Sciatica	Spinal pain	Temporaomandibular joint pain	Trigeminal neuralgia	Osteoarhtirits	Psoriatric arthropathy	Phantom limb	Post herpetic neuralgia	Learning disability
Neuropathy	1									
Sciatica	0	1								
Spinal pain	0	0.02*	1							
Temporaomandibular joint pain	0	0	0	1						
Trigeminal neuralgia	0.01*	-0.01*	0	0.02*	1					
Osteoarhtirits	0	-0.01*	0	0	0	1				
Psoriatric arthropathy	0	0	0	0	0	0	1			
Phantom limb	0.01*	-0.01	0	0	0	0	0	1		
Post herpetic neuralgia	0.02*	-0.01*	0	0	0.11*	0	0	0	1	
Learning disability	0	0	0	0	0	0	0	0	0	1
Epilepsy	0	-0.01*	0	0.01*	0	-0.01	0	0.01*	0	0
Mental illness	0	-0.01*	0	0	0.01	0	0	0	0	0
Dementia	0	-0.01*	0	0	0	0	0	0	0	0.01*
Obesity	0	0.01*	0	0	0	0.01*	0	0	0	0
Hyperthyroidism	0	0	0.01	0	0	0.01*	0	0.01*	0	0
Heart failure	0	-0.02*	0	0	-0.01*	0	0	0	0	0
Atrial fibrillation	0	-0.01*	0	0	0	0	0	0.01	0	0
Asthma	0.01*	0.01	0	0.01*	0	0.01*	0	0	0	0
Stroke	0	-0.02*	0	0	0	-0.01*	0	0	0	0

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Neuropathy	Sciatica	Spinal pain	Temporaomandibular joint pain	Trigeminal neuralgia	Osteoarhtirits	Psoriatric arthropathy	Phantom limb	Post herpetic neuralgia	Learning disability
Osteoporosis	0	-0.01*	0.01*	0	0	0.01*	0	0	0	0
Diabetes	0.02*	0	0	0	0	0.01*	0.01*	0.01*	0	0
Coronary heart disease	0	-0.01*	0	0	0	0.01*	0	0.01*	0	0
Hypertension	0.01*	0.01	0.01*	0	0	0.04*	0	0	0	0
Chronic pulmonary disease	0.01*	-0.01*	0	-0.01	0	0	0	0	0.01*	0
Chronic kidney disease	0	-0.01*	0	0	-0.01	0.02*	0	0	0	0
Depression	0.01*	0	0	0	0	0.01*	0	0	0	0
Anxiety	0.01*	0.01*	0	0	0	0	0	0	0	0

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Epilepsy	Mental health	Dementia	Obesity	Hyperthyroidism	Heart failure	Atrial fibrillation	Asthma	Stroke	Osteoporosis	Diabetes
Epilepsy	1										
Mental health	0.01	1									
Dementia	0.01*	0.02*	1								
Obesity	0	0	0	1							
Hyperthyroidism	0.01*	0	0.01*	0	1						
Heart failure	0	0	0.01*	0	0.01*	1					
Atrial fibrillation	0	0	0.02*	0	0.02*	0.12*	1				
Asthma	0.01*	0	0	0.01*	0.01*	0	0.01	1			
Stroke	0.02*	0.01*	0.04*	0	0.01*	0.03*	0.05*	0	1		
Osteoporosis	0	0	0.01	0	0.02*	0.01*	0.02*	0.01*	0	1	
Diabetes	0.02*	0.01*	0.01*	0.03*	0.02*	0.02*	0.01*	0.02*	0.01 *	0	1
Coronary heart disease	0	0	0	0.01	0.02*	0.14*	0.07*	0.02*	0.03*	0.01*	0.04*
Hypertension	0.01*	0	0	0.01*	0.03*	0.01*	0.02*	0.03*	0.02*	0.02*	0.07*
Chronic pulmonary disease	0	0	0	0	0	0.05*	0.03*	0.04*	0	0.03*	0.01*
Chronic kidney disease	0	0	0.01*	0.02*	0.01*	0.03*	0.02*	-0.01	0.01*	0.01*	0.02*
Depression	0.01*	0.01*	0	0.01*	0.01*	0	0	0.02*	0.01*	0.01*	0.01*
Anxiety	0	0.01*	0	0	0	0.01*	0	0.02*	0	0.01*	0

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

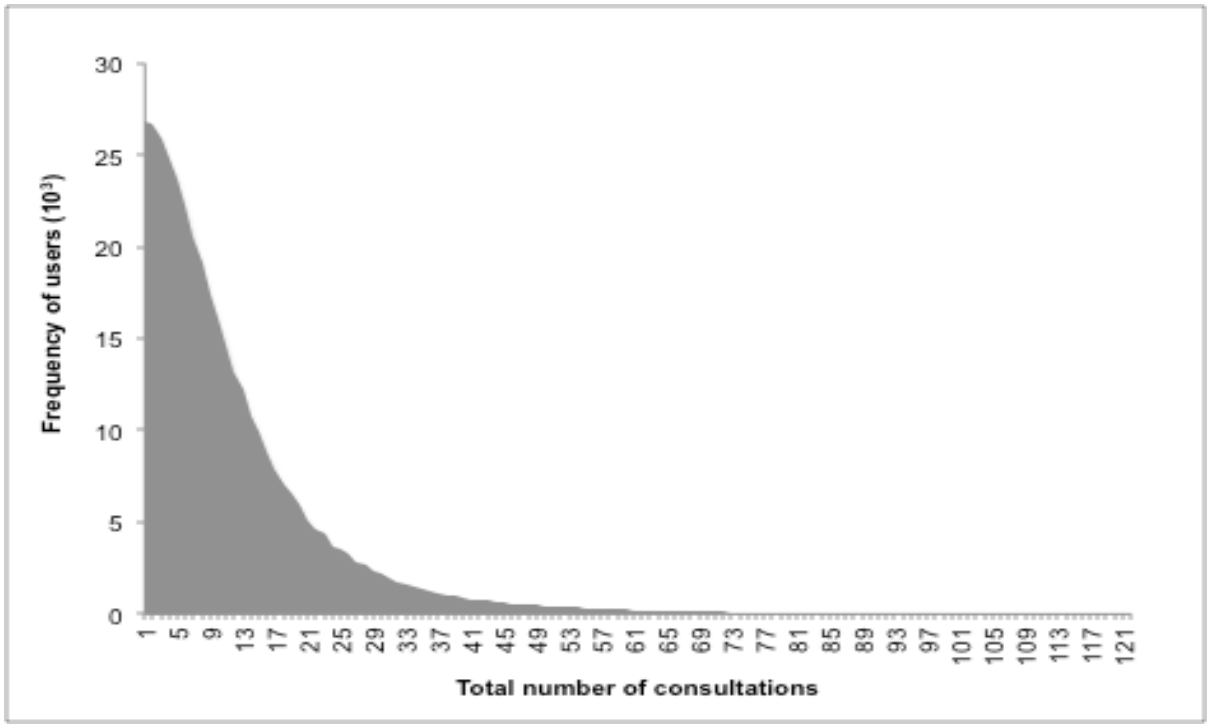
(Continued) Appendix 19 Pearson correlation analyses of variables used in GEE models

	Coronary heart disease	Hypertension	Chronic pulmonary disease	Chronic kidney disease	Depression	Anxiety
Coronary heart disease	1	1				
Hypertension	0.05*	0.01*				
Chronic pulmonary disease	0.03*	0.02*	1			
Chronic kidney disease	0.02*	0.01*	0.01*	1		
Depression	0.01*	0.01*	0.01*	0	1	
Anxiety	0.02*	1	0.02*	0	0.25*	1

Note: the correlation coefficients range from -0.000 to 0.09 indicating predominantly no or weak correlations, subject to p-values*Significance at $p \leq 0.05$

Appendix 20 Testing linearity assumption of primary care consultation data

Graphical testing in the form of histogram was used to discern whether the distribution of the primary care consultation data was normal. The distribution as shown below was negatively skewed, hence indicating a non-normal distribution. Shapiro-Wilk and Shapiro Francis test was also used to further test for variable normality. P-values of the tests were p=0.0002 and p=0.0006 respectively, which are less than the Wilk value in both tests hence confirms the non-normality distribution of consultation data.



Statistical test	**Statistic output**				
SD	69.31				
Mean	110.93				
Median	106.5				
IQR	53.5, 159.5				
Skewedness	0.01				
Kurtosis	0.36				
Shapiro Wilk	**Observations**	**W**	**V**	**Z**	**Prob>z**
Consultation data	212	0.97	4.64	3.542	0.0002
Shapiro Francis	**Observations**	**W**	**V**	**Z**	**Prob>z**
Consultation data	212	0.97184	4.819	3.264	0.00055

Appendix 21 Read codes for referrals to pain management specialist

Pain clinics or pain management service		
Medcode	**Readcode**	**Term**
1936	8H69.00	Referral to pain clinic
12160	ZL98.00	Seen by pain management specialist
13670	ZL58.00	Referral to pain management specialist
21965	ZLA2L00	Seen by pain management nurse
32539	ZL17.00	Under care of pain management specialist
32957	ZLEB.00	Discharged from pain management service
43476	ZLD2J00	Discharged by pain management specialist
46604	ZL22C00	Under the care of pain management nurse
51210	ZL62C00	Referral to pain management nurse
61554	ZLD7A00	Discharged by pain management nurse
61911	9b8F.00	Pain management (speciality)
107428	9NNh.00	Under the care of pain management specialist
107475	8HVu.00	Private referral to pain management service
10902	Z1H..00	Pain management
6899	9N1k.00	Seen in pain clinic
97767	Z1H3.11	Pain management programme
48922	Z1H3.00	Pain management programme
32674	8HTP	Referral to musculoskeletal clinic
9682	8HtH.00	Referral to back pain clinic
9682	8HTH.00	Referral to back pain clinic
12009	8HTd.00	Referral to rheumatology clinic

Appendix 22 ICD-10 codes of causes of hospital admission in clinical HES-data file

Primary cause of in-patient hospitalisation	
ICD-10 code	**Diagnosis**
A0-A99	Certain infectious and parasitic diseases
C00-C96 D00-D49	Neoplasms
D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
E00-E89	Endocrine, nutritional and metabolic diseases
F01-F99	Mental and behavioural disorders
G00-G99	Diseases of the nervous system
H00-H59	Diseases of the eye and adnexa
H60-H95	Diseases of the ear and mastoid process
I00-I99	Diseases of the circulatory system
J00-J99	Diseases of the respiratory system
K00-K95	Diseases of the digestive system
L00-L99	Diseases of the skin and subcutaneous tissue
M00-M99	Diseases of the musculoskeletal system and connective tissue
N00-N99	Diseases of the genitourinary system
O00-O9A	Pregnancy, childbirth and the puerperium
P00-P96	Certain conditions originating in the perinatal period
Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities
R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
S00-S99 T07-T88	Injury, poisoning and certain other consequences of external causes
V00-V99 W00-W99 X00-X92 Y09-Y99	External causes of morbidity and mortality
Z00-Z99	Factors influencing health status and contact with health services