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Long-term and high dose opioid medicine use in the U.K.

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Abstract

Introduction

The number of prescriptions dispensed for opioid medicines has increased in the U.K. in the last two decades and studies have shown patients are receiving opioids for longer periods than in the past. There is a lack of evidence as to the effectiveness of these drugs when used long-term, as efficacy evidence is taken from short clinical trials in populations who do not have the comorbidities commonly seen in chronic pain patients. Large observational studies of patients prescribed opioid medicines outside of clinical trials, have identified that some patients taking long-term opioids are reporting they are still in high levels of pain. There is also a concern that patients are receiving high dosages of opioid medicines without effective pain relief. However, no studies in the U.K. have looked at the proportion of patients who continue to receive opioids (for all conditions) in the long-term or at high dosages so we do not know how opioid use develops in the U.K..

Research from other countries has also identified that long-term and high dose use is linked to patient characteristics such as patient demographics and psychological and physical comorbidities. For example, a prior history of depression has been found to increase the risk of long-term and high dose use. This is of concern as this may indicate that patients may be potentially medicating the depression with the opioid. This may not be the case in the U.K. due to key factors such as the structure of the health system, so the aim of this thesis was to see if this phenomenon could potentially be occurring in the U.K.

Methods

This thesis was a retrospective observational cohort study of patients receiving opioid medicines for non-cancer conditions using data from a U.K. derived primary care database, the clinical practice research datalink (CPRD). Patients were included in the study if they received a prescription for opioid medication at any point in the year 2009 and followed,

where possible to January 2015 (though data was collected for baseline variables prior to 2009). This thesis consists of a series of longitudinal analyses that attempt to define and describe the probability of long-term use and proportion of patients who receive high dosages in the U.K and seeks to understand how baseline characteristics (such as having a comorbid condition occurring before opioid use starts) affect the probability of long-term and high dose use. Competing risks methods were used to calculate the probability of continuation of opioid medicines (using death as a competing risk) and to determine long-term use. Cox regression models were used to determine whether baseline factors (such as prior antidepressant use) were associated with discontinuation of long-term use. Calculation of odds ratios were used to predict whether baseline characteristics predicted high dose use. Cox regression was also used to predict time to discontinuation of high dose use.

Results

In the U.K., 10.58% of patients received opioid medicines to treat non-cancer pain in the year 2009. Of the non-cancer patients included in the study, 41.41% were patients who received opioids in the six months prior to 2009 and the remaining were new users of opioid medicines. In the new user opioid group, 5.75% continued to be prescribed opioids for at least one year. When including new and existing users of opioid medicines, one in thirty people in the U.K. population who started opioids for non-cancer pain in 2009 were continuously prescribed opioids for a full year. Patients who were female, received an antidepressant before opioid use started and were in the youngest age category were more likely to continue opioid use past 2 years. The probability of continuing to take opioid medicines is higher in patients who have been receiving opioids for longer and are on higher dosages; in patients who had received over 10mg OMEQ for over two years, over half of patients continued to receive prescriptions for opioid medicines for the five year period study after 2009.

In the U.K. population, one in a hundred opioid medicine users were prescribed a high dose (estimated dosage received >120mg oral morphine equivalents per day for at least 91 days)

for non-cancer pain in their first 91 days of use in the year 2009. Patients receiving high dosages were likely to be receiving multiple opioid drug types and to receive preparations with multiple release profiles.

In new users of opioid medication, the odds of high dose use were increased in patients who were younger (aged 18-49 years), had 3 or more comorbidities or were in receipt of an antidepressant or benzodiazepine and/or anti-anxiety drug before or after opioid use started. In new and existing users of opioid medicines, patients who were receiving high dosages were more likely to be diagnosed or be recorded with symptoms of depression or anxiety and to have been prescribed an antidepressant or benzodiazepine and/or other anti-anxiety drug in the youngest age group compared to the older age groups.

Of the patients that were prescribed high dosages of opioid medicines for at least 91 days, 37.64% of patients did not have a second consecutive high dose quarter due to death or stopping high dose use. Almost one in five patients who had a high dose quarter continued to have a high dose for the next three years (22.98%). Older patients, patients prescribed weak opioids and/or tramadol discontinued high dose use at a faster rate than younger patients.

Conclusion

Both high dose and long-term use were found to be associated with a prior prescribing of antidepressants before opioid use started, suggesting that in the U.K. psychological comorbidities are associated with continued and high dose opioid use. Further work is required to measure outcomes within these groups and to understand the care that these patients have already received.

Most patients who start opioid medicines in the U.K. stop taking them in their first year of use. However, of those who continue use past two years, a large proportion continue for the full five year period. Similarly, only a small proportion of patients receive high dosages of opioid medicines but once this use is established, many patients have a high probability of

continuation. Further work should be undertaken to facilitate effective review of these patients in practice.

Publications

Preliminary work associated with the development of this thesis was presented at the following conferences:

Jane Harvey, Roger Knaggs, Li-Chia Chen. Strong opioid utilisation within UK primary care: A longitudinal cohort study of non-cancer strong opioid users. Poster and Podium Presentation, British Pain Society Annual Scientific Meeting, 30 April 2014 at Manchester Central Convention Complex, Manchester, UK. [First prize of trainee oral presentation]

Jane Harvey, Roger Knaggs, Li-Chia Chen. Prevalence of Long-term Strong Opioid Utilisation for Non-Cancer Pain in the UK Primary Care. Poster Presentation, EuroDURG 2014 Scientific Meeting, 27 to 29 August 2014 at University Medical Centre Groningen, Groningen, Netherlands.

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List of abbreviations and acronyms

aHR	Adjusted Hazard Ratio
aOR	Adjusted Odds Ratio
BNF	British National Formulary
CCG	Clinical Commissioning Group
CI	Confidence Interval
CMD	Common Mental Disorder
CNCP	Chronic Non-Cancer Pain
CPRD	Clinical Practice Research Datalink
CSR	Cochrane Systematic Review
DDD	Defined Daily Dose
GP	General Practitioner
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
ISAC	Independent Scientific Advisory Committee
NDD	Numerical Daily Dose
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNT	Number Needed to Treat
NPSAD	National Programme on Substance Abuse Deaths
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds Ratio
OMEQ	Oral Morphine Equivalent
ONS	Office National Statistics
PPV	Positive Predictive Value
QOF	Quality and Outcomes Framework
RCT	Randomised Controlled Trial
RMDQ	Roland Morris Disability Questionnaire
SF-12	Short Form-12
SF-36	Short Form-36
SIGN	Scottish Intercollegiate Guidelines Network
TCA	Tricyclic Antidepressant
uHR	Unadjusted Hazard Ratio
uOR	Unadjusted Odds Ratio

Chapter 1. Introduction and outline of chapters

1.1. Introduction to thesis

Opioid use, in terms of number of prescriptions and the length of time individual patients are receiving opioid medicines for, has increased in the past 2 decades in the United Kingdom with an increase in the prescribing of opioid medicines to treat chronic non-cancer pain [1, 2]. The evidence for efficacy of opioids in the long-term is lacking as blinded randomised controlled trials are short term (max 15 months for chronic back pain) [3] and a large proportion explicitly exclude patients with a history of psychiatric illness (Section 2.6.2). When patients taking opioids are studied outside of clinical trials (Section 2.7), it is found that a high proportion of patients are still in high levels of pain and so it is possible that treatment of chronic pain with opioid medicines is not always achieving the primary aim that patients want from chronic pain treatment, an improved enjoyment of life [4]. Conversely, some patients report that the pain relief they receive from opioids is greatly beneficial [5] and studies (albeit ones of low quality) have found that a small proportion of patients continue to receive benefits in the long-term [6]. Therefore, the use of opioid medicines to treat chronic pain divides opinion.

In the U.K., doctors have expressed the concern that opioid use may sometimes be inappropriate, in that, “in many cases, doses are too high and treatment is too long” [7]. This shows a suspicion amongst doctors that improvements can be made in the use of opioids to treat chronic pain, but that research is needed to quantify and understand what the improvements should be. A qualitative study has identified many issues associated with the current level of care received by patients taking opioid treatment, that chronic pain treatment is lacking and that primary care prescribers lack confidence when treating patients with chronic pain [8]. An additional problem is that prescribers may follow the World Health Organisation’s (WHO) pain ladder which encourages dose increases in uncontrolled pain [9]. This is appropriate in the treatment of cancer pain but may not be so in the treatment of chronic pain. In the treatment of chronic pain, following this guidance may encourage the use of high dosages of opioids to treat high pain intensities in chronic pain patients when this may not lead to substantial reductions in pain and/or improvements in quality of life [10].

In the U.S.A., it has been identified that patients who have a history of mental health disorders are more likely to be prescribed opioids, take opioids for longer periods and receive higher dosages of opioids; the riskiest patients using the riskiest regimes (high dosages) [11]. It has been suggested that this is because patients "self-select" for long term use [12]. This has been called the "adverse selection" of certain types of patients receiving opioid medicines. This may be inappropriate because patients may be medicating their depression with opioids or receiving opioids in isolation of other treatments for chronic pain or continuing to receive opioid medicines at higher and higher dosages in the quest for adequate relief [13].

The U.K. is different to the U.S.A. in terms of many factors that may affect the use of opioids [14]. For example, the healthcare system is centralized, publicly funded and prescribing of controlled drugs monitored closely. This means patients are less likely to be able to "doctor shop" as they are usually registered with one surgery. However, though these conditions mean that abuse and overdose is currently less likely, it is still possible in the U.K. that patients are receiving long term or higher dosages of opioids due to mismanagement of pain, for example, due to the presence of concurrent mental health conditions. This is especially likely when alternative treatments are not readily available.

In the U.K., no studies that include all opioids report how the probability of continuing to take opioid medicines changes over time, the influence of dose and the effect of psychological comorbidities such as pre-opioid diagnosis of depression on long-term use. No studies have measured the dosage received by patients and related high dose use to patient factors such as common psychological comorbidities occurring before opioid use starts.

Therefore the aim of this PhD is to describe the prevalence of long-term and high dose use and to describe how different factors influence the use of long-term and high dose opioids.

The objectives are:

- Define a cohort of patients receiving opioids for non-cancer pain

- Determine a definition of long-term use and see how factors relate to discontinuation of patients taking opioid medication
- Determine the dosages of opioid medication patients are prescribed, the regimes they use at various dosages and see how dosage influences long-term use
- Determine how factors are related to whether patients receive high dosages and the characteristics of patients who receive high dose opioids and long-term high dose opioids

The content of the chapters of this thesis are as follows:

Chapter 2 includes the literature to support the argument made in this introduction. An overview of the size, content, strengths and weaknesses of the clinical practice research datalink (CPRD) is also provided as this was the source of the data used within this thesis.

Chapter 3 describes the extraction of a cohort of patients from CPRD who are prescribed opioids. Within this chapter, a comparison of the prevalence of use, opioid drugs types used and characteristics of the cohort is made between the current cohort and other sources. The suitability of the data for use is also determined.

Chapter 4 develops the methodology for analysing the probability of continuous opioid use in new and existing users. The relationship between the patient characteristics reported in Chapter 3 and probability of continuation of opioids in the long-term is assessed.

Chapter 5 describes the methodology for calculating dosages, the proportion of patients who receive different dosages, the combinations of drugs and drug formulations used within dosage bands and the probability of continuous use based on past use and dosage band.

The final analysis chapter, **Chapter 6**, contains two studies, the first, conducted using data from new opioid users examines whether baseline characteristics are linked to the probability of high dose use, and the second reports the characteristics of patients who begin high dose use during the study follow up period. In this second study, the probability of continuation of

high dose is calculated (with psychological comorbidities described in a subgroup analysis by age) and factors associated with continuation of high dose in the long-term analysed. This is to see whether patient characteristics are associated with high dose use.

Finally, **Chapter 7** contains a summary of the key findings, overall limitations of the thesis and recommendations for practice, policy and research.

Chapter 2. Literature Review

2.1. Introduction

Following a section outlining the methods of this chapter, this literature review starts with a basic outline of what opioid medicines are, the legislation governing their use in the U.K., the challenges associated with the classification of the many different opioids that are currently on the market and the possible reasons for the increase in numbers of prescriptions of opioid medicines in the U.K.. Then, the problems with the evidence for the use of opioid medicines from randomised controlled trials are discussed and the concerns as to the effectiveness of opioids raised by studies that report outcomes in the general population highlighted. Next, there is a discussion regarding the evidence that suggests that in other countries patients with psychological disorders may be more likely to receive opioids for longer periods at higher dosages and how this may be likely to be associated with inappropriate use. It is then argued that the current conditions in the U.K. may have possibly led to similar inappropriate prescribing. The adverse events associated with opioid use are discussed to show the risks associated with opioid use. The risks associated with the concomitant use of benzodiazepine medicines with opioid medicines are also considered. Based on this discussion, the aims and objectives of this thesis are then outlined. Finally, there is a description of the database that is used in this study.

2.2. Methods of the literature review

The literature review was compiled using various methods of searching the literature. This was an iterative process that continued throughout the PhD.

2.2.1. Review of Cochrane Systematic Reviews

At the start of the PhD a review of all Cochrane systematic reviews of the use of opioid medicines for chronic pain was conducted, this was to provide information on the limitations on the data from randomised controlled trials. This was conducted by retrieving articles selected from a search from a search of the Cochrane Library using the search terms:

- Analgesics, Opioids MeSH Heading Exploded

  Using radio button selected Cochrane reviews from results

- Free text opioids title and abstract search reviews using radio button for Cochrane
- Free text all opioids and NHS centre for review and dissemination systematic review search provided Cochrane on radio button.

2.2.2. Continuous monitoring of literature concerning the use of opioid medicines for chronic use

RSS feeds were set up (in 2014 through to the end of the PhD)) to continuously retrieve articles with the following search terms:

- Pubmed

  “clinical practice research database”

  “general practice research database”

  “database opioid england”

  “database opioid* england”

  “database opioid united kingdom”

"opiate database united kingdom"

"opioid noncancer"

"opioid non-cancer"

"opioid nonmalignant"

"opioid non-malignant"

"opioid long-term"

"opioids and "non-cancer""

- Embase

"opiate database united kingdom"

"opioid database united kingdom"

The additional Embase search was to ensure that all papers that were related to database research concerning opioid medicines in the United Kingdom were identified. This was to ensure that any abstracts of research that was directed related to the PhD were identified. These feeds were continuously reviewed and any relevant papers were retrieved and considered for inclusion in the literature review.

2.2.3. Identification of papers that were based on U.K. data

Pubmed/Embase was searched (using the search terms above that relate to U.K. based studies including the CPRD search terms) and the results reviewed to identify any papers (pre 2014) that were related to U.K. based studies.

2.2.4. Searching using papers identified as highly relevant

The Pubmed "similar articles" function was used to look for other papers related to key U.K. based studies such as those by Foy, Bedson.

2.2.5. Identification of papers from known U.K. authors

Notifications from Pubmed were set up to identify when key U.K. based authors (Foy, Bedson) released papers.

2.3. Basic information about opioid medicines

2.3.1. Definition and mechanism of action

Opium is the mix of alkaloids extracted from the poppy seed (*Papaver somniferum*) whilst the term 'opiate' refers to alkaloids such as morphine and codeine that are found naturally within the extract [15]. Encompassing all natural and synthetic compounds, the term opioid refers to any pharmacological agent that binds to opioid receptors whose effects are blocked by antagonists like naloxone [16].

Opioids exert their actions via binding to G protein coupled opioid receptors of which there are three subtypes MOR (μ opioid receptor), DOR (δ opioid receptor), and KOR (κ opioid receptor) with analgesic effects generally mediated by the μ receptor. These receptors are distributed throughout the brain, spinal cord and periphery [16]. Binding of opioids to receptors causes the opening of potassium channels and inhibition in the opening of calcium channels. These effects decrease neuronal excitability through hyperpolarisation of the membrane and inhibition of excitatory neurotransmitter release (for example glutamate) [15].

Opioids produce analgesia via inhibition of the transmission of pain signals at the spinal cord level. This is through activation of serotonin and encephalin mediated descending pain pathways which inhibit transmission of pain signals within the dorsal horn of the spinal cord. Opioids also have a direct inhibitory action via presynaptic inhibition of afferent nociceptive neurons within the dorsal horn of the spinal cord. Opioid receptors present in the periaqueductal grey matter and nucleus raphe magnus in the midbrain region also cause inhibition of pain signal transmission via activation of descending inhibitory pain pathways from the brain [16].

2.3.2. History of use and legislation governing opioid use

Opioids have been used for thousands of years to reduce pain and aid sleep. Cultivation of poppy seeds were recorded by the Sumerians as long ago as 5,000 BC [17]. Opioids have also been used recreationally and references to opium use and its beneficial and ill effects

can be found throughout history. In the 18th and 19th centuries, opium use was uncontrolled in the United Kingdom and it was freely available for sale until restriction to medical use only under legislation in the early 20th century [17]. Drug legislation in the U.K. underwent further transformation and culminated in The Misuse of Drugs Act 1971 which classified and restricted the use of illegal substances, and are the laws governing illegal drug use today [18]. Though these laws restrict the use of opioids in society, physicians are still able to prescribe such drugs under the Misuse of Drugs Regulations 2001. These regulations allow all doctors, independent prescribers and supplementary prescribers to prescribe opioids for pain [18].

In addition to these key policies governing the use of controlled drugs, further legislation also governs the use of controlled drugs; these regulations were introduced as a result of the Shipman Enquiry. Harold Shipman was a GP who was convicted of the murder of 15 of his patients. He carried out the murders by using lethal doses of the opioid diamorphine. The Shipman Enquiry was an independent enquiry ordered by the Secretary of State for Health in the year 2000 to make recommendations as to "what changes to current systems should be made in order to safeguard patients in the future" [19]. Following the Shipman Enquiry, the Health Act 2006 required all healthcare organisations that use controlled drugs to have an "accountable officer" responsible for supervising and managing controlled drugs within the organisation. Accountable officers monitor procedures for the management of controlled drugs and ensure the volumes of controlled drugs prescribed within their organisations are monitored via electronic prescribing data. Controlled drugs are divided into schedules which are defined by restrictions on prescribing. For example, the Department of Health and Scottish Government introduced a strong recommendation that prescribers only prescribe enough medication for a 30-day supply for drugs in Schedules 2, 3 and 4 [18]. In the U.K., compared to other countries, there are relatively tight controls on controlled drug prescribing [20].

2.3.3. Classifications of opioids

Opioids can generally be classed as weak or strong opioids, this was originally based upon their affinity for their receptor and so should be related to their analgesic effect [21]. However, this is not an exact definition and a number of highly referenced sources of information group opioids as weak or strong using different criteria. For example, in the Scottish Intercollegiate Guideline Network (SIGN) [22] 2013 guideline for the Management of Chronic Pain, tramadol is classified as a weak opioid (due to receptor binding and the fact the British National Formulary (BNF) states a maximum dose for the drug) whilst the BNF [23] states that tramadol is a strong opioid. In March 2015, tramadol was reclassified as a Schedule 3 opioid due to an increase in the number of deaths attributed to the drug in recent years and so in the case of the BNF, it may be that the drug is stated as a strong opioid in order to make prescribers aware of the dangers of tramadol use.

Opioids are available in the U.K. in many different drug types and formulations [23]. The affinity and efficacy that a drug has in relation to their receptor is related to their clinical effect. However, the clinical effect of the drug can be controlled to some extent (as this will vary from patient to patient) via the dosage at which it is administered. The efficacy of a certain dose of opioid to relieve pain is recognised in terms of Oral Morphine Equivalents (OMEQ). Relative opioid potencies are usually calculated within clinical trials by administering an opioid at varying dosages and comparing the effects of the medication to another opioid at varying dosages (usually morphine) using pain scores (pain severity and pain relief) [24]. The ratio between the amount of drug required to produce the same effect is then calculated by plotting the assay results and comparing the differences. The ratio calculated from these studies can then be used to compare dosages between different opioids. Though these figures can vary from one source to another, OMEQ are commonly used in opioid cohort studies to determine the relative exposure of the cohort to opioid medication within a cohort of patients that receive different opioid types, where authors report what conversion factor was used [25].

In an abstract which reports a study in which U.K. GPs (n=22) ranked analgesics [26] and came to a consensus on which analgesics were equipotent and then ranked grouped analgesics due to potency, some strong opioids were in lower categories than weak opioids, for example buprenorphine 5-10microgram/hr patch was ranked as a “moderate opioid” whilst codeine 30mg, dihydrocodeine 30mg and tramadol 50mg were ranked above this as “strong opioids” (morphine and oxycodone were ranked as “very strong analgesics”). Buprenorphine 10 microgram/hr patches are equivalent to 24mg OMEQ/day which is a similar dosage to 240mg codeine (equivalent to 24mg OMEQ/day) (the maximum daily dosage) [25]. Though this study was very small and developed by consensus methods (though differing opinions may occur), the abstract at least highlights the possibility that GPs do not appear to group opioids based purely on strong and weak opioid categories alone. Thus, there is a lack of consensus over the classification of opioids and the range of OMEQ can overlap between weak and strong opioids.

Researchers in the U.K. have previously used various criteria to describe opioid use e.g. including strong opioids only in the inclusion criteria [2], reporting the use of more tightly controlled opioids (scheduled 2 or 3 opioid use) [1], grouping opioids use into strong and weak categories (including tramadol in the weak group and in the strong group) [27, 28]. The use of the weak and strong classification is useful to some extent as this categorisation is generally referred to by a variety of reference sources, except in the case of tramadol, and gives a rough indication of strength. Studies which include tramadol should consider including this drug as a separate category. Additionally, these categories (strong and weak or a particular schedule) do not relate to the OMEQ consumed by patients or the order in which GPs rank opioid strength. Therefore, further classifications based on OMEQ should also be included within a study in order to more accurately measure the amount of analgesia received by a patient.

2.4. The increase in the use of opioid medicines in the U.K.

This section discusses the increase in the number of prescriptions dispensed in the U.K. and how this translates into changes in patterns of opioid use by individual patients.

2.4.1. Increases in the numbers of prescriptions for opioid medicines dispensed in England

Prescription data show an increase in prescriptions for most types of opioid medication. Data regarding the number of prescriptions for opioid medicines is openly available from 2004 onwards for prescriptions dispensed in England [29-36]. The number of prescriptions for opioid medicines has increased by one third from 30.0 million in 2004 to 41.7 million in 2016 (Figure 1). The most commonly dispensed drug has been codeine (including codeine prescribed alone and in combination with paracetamol ("co-codamol")) since 2004. In 2016, more than one in three prescriptions were dispensed for this drug (37.58%). The second most commonly dispensed opioid was tramadol (17.58%). Prescriptions for co-codamol and tramadol steadily increased from 2004, however, tramadol prescriptions have reduced since 2014 after a change in the legal classification of tramadol [37].

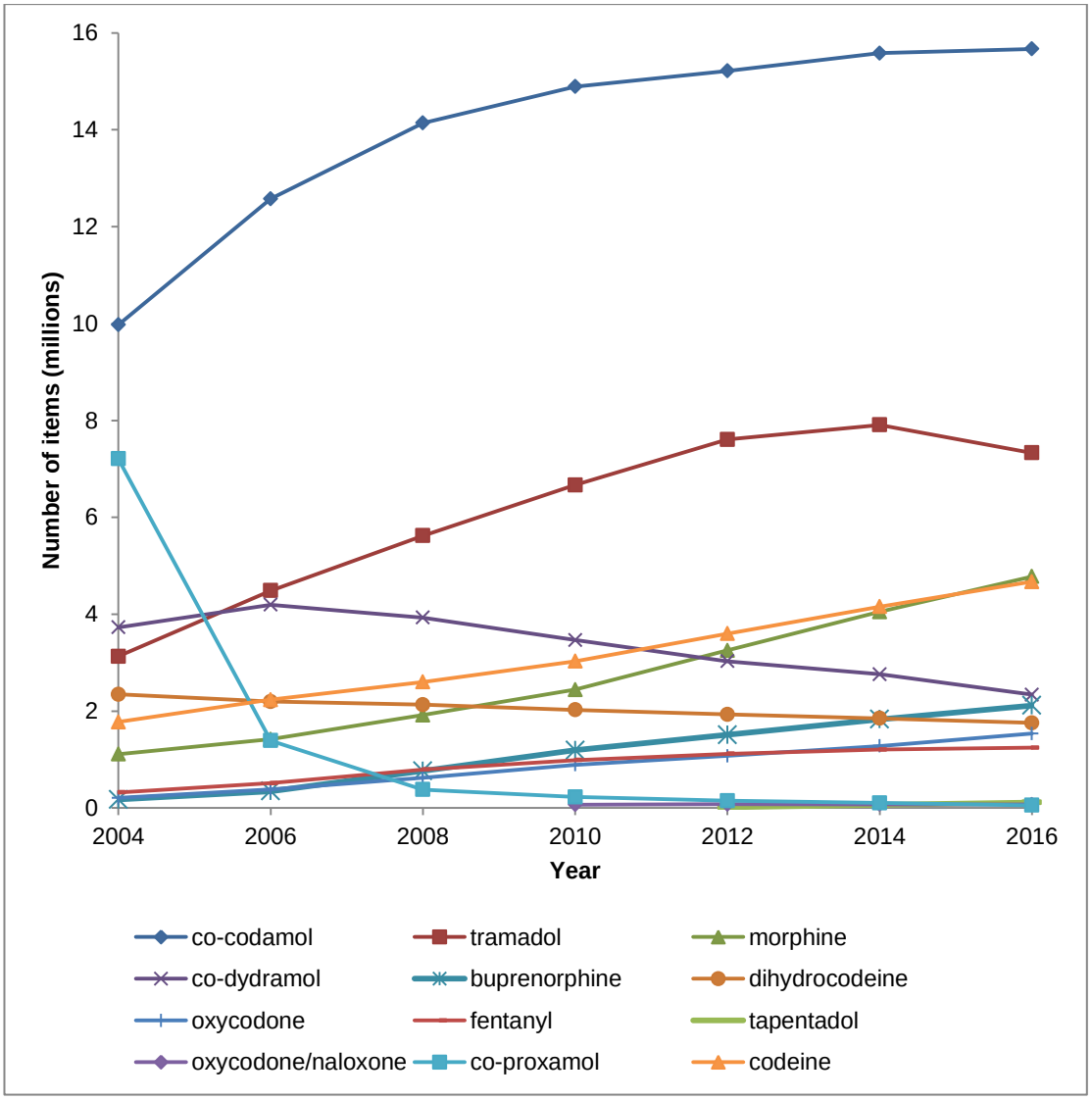
Large increases in the number of prescriptions for the more potent opioids, especially morphine and buprenorphine, are found over the 12 year period. Rises in oxycodone and fentanyl prescribing are also seen, though these drugs represent a small total proportion of opioid use (Figure 1). [29]

The opioid medication with the largest decline in prescriptions is co-proxamol. In 2004, co-proxamol was the second most commonly prescribed opioid (In data from prior to 2004 it was actually the most commonly prescribed opioid [38]). This dropped sharply due to the removal of co-proxamol from the market during the years 2005-2008. Co-proxamol is an opioid and paracetamol combination product in which the opioid component is the weak opioid dextropropoxyphene. This product was withdrawn from the market in January 2005 with a full withdrawal occurring by 2008 due to the fact this drug had been linked to a high

risk of overdose. Co-proxamol was a very commonly prescribed weak opioid combination. The withdrawal of co-proxamol is likely to have had a substantial impact on opioid prescribing patterns with different and possibly more potent drugs (in terms of morphine equivalents) being prescribed in its place.

Bedson et al 2013 [39] reported that withdrawal of co-proxamol and the series of recommendations to limit the use of cox-2 inhibitors and non-selective Non-steroidal anti-inflammatory drugs (NSAIDS) released by the Medicines and Healthcare products Regulatory Agency (MHRA) at a similar time from 2004-2006 was linked to an increase in prescribing of “moderate analgesics” including codeine, dihydrocodeine and buprenorphine. Thus in the past decade, the number of prescriptions for opioids and types of opioids prescribed have changed dramatically.

Figure 1 Number of items of opioid medication dispensed in England 2004-2016



NB The data taken from this figure was taken from the following references [29-36]

In 2016, £384 million was spent on opioid analgesics. This was approximately one fifth of the total amount spent on items dispensed under the Central Nervous System chapter of the BNF and around 4% of the total NHS expenditure on prescriptions [29]. Although prescribed at lower volumes, the costs for opioids such as off licence co-proxamol, oxycodone alone/combination tapentadol, fentanyl and buprenorphine are high, due to the fact they have a larger unit cost (Table 1). Unlicensed co-proxamol use is particularly expensive.

Thus, treatment with some opioid medications, which potentially continue long term, is not inexpensive, and therefore should offer good outcomes in terms of management of the conditions that they are used to treat.

Table 1 Cost per item for opioid medications in 2016 in England

Opioid drug	cost (millions)	items (millions)	cost/item
co-proxamol	9.0	0.1	159.2
oxycodone/naloxone	5.1	0.1	69.8
tapentadol	5.5	0.1	47.8
fentanyl	55.2	1.2	44.3
oxycodone	51.8	1.5	33.7
buprenorphine	65.0	2.1	30.7
morphine	35.3	4.8	7.4
tramadol	39.9	7.3	5.4
co-codamol	83.0	15.7	5.3
dihydrocodeine	8.4	1.8	4.8
co-dydramol	9.8	2.3	4.2
codeine	15.8	4.7	3.4

2.4.2. Patterns of opioid use from studies using patient level data

2.4.2.1. The proportion of patients receiving an opioid in the U.K.

It is difficult to tell from prescribing data the number of patients that receive an opioid medication because prescription lengths vary, patients may receive several opioid formulations or types (i.e. more than one simultaneous prescription per patient) and receive opioids for different periods of time. Therefore, data in which prescriptions can be linked together for individual patients is required to calculate prevalence estimates. Prevalence estimates are useful as they the proportion of the population likely to be affected by the use of opioids. This information can be used for future planning of healthcare provision or as a basis for further research.

Using patient level data, where prescriptions could be linked to individual patients, two studies [27, 28] compared the increase in the prevalence of all opioid use, in two different populations in the U.K. (Ruscitto [28] Tayside Scotland and Foy [27] Leeds/Bradford England). Foy [27] excluded patients who were coded as having a recent cancer diagnosis. Both studies identified that the prevalence of opioid prescribing had increased. This was from 8.5%-11.0% 1995-2010 in the Scottish study and 6.60%-12.78% 2005-2011 in the Leeds/Bradford study; these studies show in two different U.K. populations that by 2010, just over one in ten people in the U.K. received an opioid prescription.

Another recent study using data from the Clinical Practice Research Database (CPRD) [40], which contains primary care prescribing data and covers selected practices from the whole U.K found that the prevalence of opioid use had increased from 2.5% 2000– 5.0% 2015. This is somewhat lower than the previous two studies and this is most likely due to the fact this study did not include compound opioid analgesics (including co-codamol), which contribute a large proportion of current opioid prescriptions (Figure 1).

In addition to reporting prevalence of all opioids, studies have reported differing increases in weak and strong opioids. Foy [27] identified an increase in the proportion of patients prescribed weak and strong opioid prescriptions (weak 6.53%-12.41%, strong 0.13%-0.85% 2005-2011), whilst Ruscitto [28] observed a small decrease in the proportion of patients prescribed weak opioids (8.4-8.2% 1995-2010) and an increase the proportion of patients prescribed strong opioids (0.24%-3.6% 1995-2010). This difference is likely due to the fact tramadol was classed as a weak opioid in the Foy study and a strong opioid in the Ruscitto study. Ruscitto found that 0.8% of patients received a strong opioid in 2010 when tramadol was excluded, which is more in agreement with Foy. Another repeated cross sectional study, using data from CPRD, found that the proportion of patients receiving strong opioids increased from 0.18%-0.92% 2000-2010 [2]. Overall, these studies show that the prevalence of weak opioid use, when tramadol is classified as a strong opioid, has not increased to a great extent whilst the use of strong opioid medication has increased significantly.

2.4.2.2. Increases in long-term use of opioid medicines

Increases in the numbers of prescriptions for a drug in a year can be due to increases in the numbers of patients initially prescribed the drug (either more patients having a particular illness or a lower threshold for prescribing a particular drug or evidence that a drug is effective for an additional condition) or an increase in the dose or overall continuous length of use of the drug. The studies that look at prevalence do not distinguish between increases in new and existing users as they are cross sectional studies and are looking at each year in isolation. However, a number of other studies (as detailed below) have identified that opioid medication use has increased due to an increase in the use of opioids for longer periods.

Bedson [1] compared the rates of long-term opioid prescribing (defined as receiving at least 3 or more prescriptions in a 90 day period) in patients that had not received opioids in the year before between 2002 and 2013 in patients with musculoskeletal conditions. Though the study only included patients with non-cancer related musculoskeletal conditions, the study used CPRD data from the whole of the U.K. and so still included a large sample size. The analysis showed that over the course of the study, there was an initial increase in the annual rate of patients receiving long-term opioid prescriptions, though this trend became stable in 2009 and actually reversed slightly by the end of the study (between 2002-2009, an increase from 42.4-58.3 per 10,000 person years remaining the same until 2011 and then decreasing to 55.8 per 10,000 patient years in 2013). This study shows that over the study period, more people were receiving long-term opioid therapy for non-cancer musculoskeletal conditions.

Cartagena Farias et al 2017 [40] also used data from CPRD to examine the proportion of all patients receiving opioid medication. This study was not restricted to patients with musculoskeletal conditions. The study measured the average length of continuous opioid use and found that the average continuous length of continuous prescribing periods increased from 64 days in 2000 to almost double that to 102 days in 2015. This change was not seen in the other drugs of misuse measured in this study e.g. benzodiazepines. As this study excluded combination products (the vast majority of codeine products), this would

have predominately included the stronger opioids. This is similar to the finding by Zin [2] that the number of prescriptions per patient per year increased from 5.7-9.4 between 2000-2010 when looking at prescriptions per patient for the strong opioids buprenorphine, morphine, fentanyl and oxycodone. Thus, in addition to more patients taking opioids, they are also taking them for longer.

2.4.2.3. Use of more potent opioid medication

Bedson et al. [1] also found that the likelihood of receiving long acting controlled opioids in the first 90 days of opioid treatment increased over time (2.3-9.9% 2002-2013). In patients who were receiving opioids for at least 2 years, the study found that the likelihood of receiving long-acting controlled opioids increased from 3.5 - 22.6% 2004-2013.

2.4.2.4. Summary

These studies show that, by the end of the last decade, the use of opioids for longer periods had increased, that more potent opioids are used earlier on in treatment and that they were used for longer periods over time and that the increase was at least in part due to the increase in use of opioids for non-cancer pain.

2.5. The use of opioid medication to treat chronic pain

2.5.1. The prevalence and impact of chronic pain

Chronic pain defined as “pain present for 3 months or greater” is estimated to affect between one third to a half of people in the U.K., with 10.4-14.3% suffering from moderate to severely disabling chronic pain [41]. The prevalence of chronic pain rises in certain populations. For example, half of people with a long-term condition suffer with chronic pain whilst 80% of patients with three or more conditions suffer with chronic pain [42]. Chronic pain is more prevalent in older populations with 62% of the population over the age of 75 reporting chronic pain symptoms. In comparison, approximately 30% of adults aged under 40 reported chronic pain [41].

Chronic pain, at its worst, has a huge impact on sufferers, interfering with sleep, ability to work and relationships with family and friends [43]. “Well-being” scores measured in chronic pain sufferers in the health survey for England found average scores in patients with the most disabling form of chronic pain were similar to the scores of the lowest 10% of those who didn’t report pain. 70% of men and 68% of women with the most disabling form of chronic pain were anxious or depressed [44]. One large European based telephone survey with almost 50,000 respondents with chronic pain found that 16% of patients felt the pain was so bad they wanted to die [45]. The presence of severe long-term chronic pain has been associated with an increased risk of death which has been shown to be independent of measured socio-demographic factors and patient reported long-term co-morbidities [46]. Thus, chronic pain has a huge impact on a patient’s quality of life.

Outcomes from all treatments of chronic pain are on the whole poor, with medications used for chronic pain having low efficacy [47]. Alternative, non-drug psychological treatments suffer from poor quality of evidence [48]. Therefore, the idea that opioid medications, that when used for acute pain confer potent analgesia (e.g. NNT 2.9 10mg IM morphine for post-operative pain) [49], could offer hope of an improved quality of life for these patients, was an idea that was embraced both in the U.S.A and other countries including the U.K.

2.5.2. The rise in use of opioids for chronic pain; moving from acute and palliative care to chronic pain

Opioids are primarily used to treat pain. Pain is a symptom of many conditions and it occurs in different clinical situations such as acute pain, chronic pain and palliative pain. At the beginning of the 1990's, opioid use was accepted to be used in palliative situations and for acute pain. However, it was generally thought that opioids did not work for other types of pain and that the risks outweighed the benefits [50]. Increasing awareness of painful conditions [51], reports that opioid addiction rates were low [52] (evidence which has since been heavily criticized) [53], and aggressive marketing from pharmaceutical companies [54] encouraged a greater use of opioids and it was shown that, within the U.S.A., non-cancer pain was one of the main reasons for the increase in prescribing [55]. As mentioned in the previous section, the rise in strong opioid use has also been shown to be due to the increase in treatment of non-cancer pain in the U.K, though there is little evidence as to the effectiveness of opioids in the long-term.

2.6. Evidence for the use of opioids for non-cancer pain

In this section, the limitations of the results of randomised controlled trials (RCTs) and open label extensions of RCTs that evaluate the use of opioids for chronic pain are discussed.

Many systematic reviews (including Cochrane reviews in a large range of diseases) have been conducted that consider the efficacy of opioid medication for common non-cancer conditions: low back pain [3, 56, 57], osteoarthritis [58], neuropathic pain [59-64], rheumatoid arthritis [65] and chronic pain in general [66, 67]. The results of these systematic reviews usually identify that a proportion of patients may obtain clinically significant levels of pain relief. For example, trials of patients taking opioid medicines versus placebo have found that patients receiving opioids for low back pain were found to be more likely to obtain 30% pain relief (OR 1.91 1.41-2.58) [3] and the NNT for the use of oxycodone in neuropathic pain (specifically painful diabetic neuropathy) is 5.7 (4.0-9.9) for “moderate benefit” [62]. However, the reviews also state that trials are usually of very poor quality (due to high numbers of drop outs) and these results are subject to a number of limitations.

These limitations include (1) the fact that outcomes are usually limited to a measure of pain intensity rather than functional outcomes (Section 2.6.1), (2) the issue that trials are likely to exclude patients with a history of psychiatric disease and other physical comorbidities (Section 2.6.2) and (3) that trials are short (Section 2.6.3).

2.6.1. Trials do not measure quality of life and other outcomes that are important to patients

The aims of treatment in chronic pain would ideally be to remove pain completely, enabling the patient to conduct their life as any other patient would, automatically leading to an improvement in function and quality of life, if adverse effects did not impede this process. However, studies that look at chronic pain show that many patients will receive only modest benefits from most treatments, including opioid treatment, and therefore a benchmark of the lowest acceptable improvement in a particular outcome must be set to enable prescribers

and patients to make a relatively objective decision as to whether the continuation of the treatment is beneficial. The “Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has expressed the need for outcomes in RCTs to include multiple criteria in addition to assessing the efficacy of chronic pain medicines, including both pain intensity scores and measures of physical and emotional functioning [68].

To this end, the IMMPACT group also conducted a study as to the outcomes that patients with chronic pain describe as the most important outcomes from pain treatment. The most important outcome reported by patients was “enjoyment from life,” closely followed by levels of “fatigue” [4]. The IMMPACT recommendations state that physical and mental function should be measured in trials of opioids for chronic pain to assess whether this is the case. They recommend the use of several tools including the short form – 36 (SF-36) measure. The U.K. guidelines therefore emphasize the need to see an improvement in not only pain outcomes but also activity levels and sleep [69]. A systematic review (searches conducted April 2016) of the physical and mental components of the SF-36 measured within randomised controlled trials of opioids for chronic pain found that although significant differences were found in the physical component score, no statistically significant difference was found in the mental component score in the opioid group compared to the placebo group [70].

2.6.2. Trials exclude patients with comorbidities

In the Cochrane systematic review of opioid therapy for low back pain, six of the 15 trials explicitly excluded patients with a history of psychiatric illness [3]. In trials for morphine for neuropathic pain, 3 out of 4 trials excluded patients with a psychiatric history [60], whilst in trials of the use of tramadol for neuropathic pain, 3 out of 6 studies excluded patients with psychiatric history [63], none of the 4 trials for oxycodone excluded patients with a psychiatric history [62] and the one study for fentanyl use in neuropathic pain did not exclude patients with psychiatric history [61]. Thus, in a number of systematic reviews, patients were

not included if they had a mental health comorbidity – a very common occurrence in chronic pain. The impact of this selection is discussed in later sections.

2.6.3. Randomised controlled trials are short, though evidence from open label trials has shown that some patients can benefit from treatment in the long-term

The majority of trials within Cochrane systematic reviews last for 12 weeks with the longest trial being for 15 weeks in low back pain, 24 weeks in osteoarthritis and 12 weeks in neuropathic pain [3, 58, 59]. Open label extension studies have been conducted to follow up patients from randomised controlled trials. A systematic review [6] of open label extension studies for all chronic pain types has been conducted and identified 11 studies in which patients had been followed up in this way. Average doses did not exceed 120mg OMEQ/day. Open label extension studies last for up to three years (one study), though the median length of open label trial is 26 weeks. By the end of this period (in the open label trials), 71.5% of the patients that were originally randomised had ended treatment. However, the results of this trial find that some patients do achieve significant benefit in that the systematic review reported there was no significant change in pain intensity between the end of the randomised period to the end of the open label phase in 6 studies with 1360 participants [6]. These trials in general had a high risk of bias (in addition to being open label) with all quality of trial indicators (selection bias, allocation concealment, incomplete outcome data, confounding bias and funding bias) not met except for selective reporting. Therefore, this group is an extremely selective population and may not be representative of real world opioid use.

2.6.3.1. Opioid efficacy may decrease because of tolerance and hyperalgesia

Analgesia from opioids may not be sustained because of the effect of tolerance and hyperalgesia. Tolerance is defined as “a decrease in the effect of the drug despite a constant dose, or a need for increased dose to maintain a stable effect” [71]. Tolerance can occur after one administration of opioid and occurs due to pharmacokinetic mechanisms, for example, the drug may induce its own elimination, or by pharmacodynamic mechanisms

such as receptor desensitization or down regulation [72]. However, tolerance can be dependent on psychological factors such as mood, which can also produce withdrawal [71]. Tolerance develops to the analgesic and euphoric effects of opioid medication and may be one of the reasons a patient requires a dosage increase. If a patient develops tolerance to medication and is not able to increase the dosage, then a patient may develop symptoms of withdrawal [73].

Opioid induced hyperalgesia is a condition defined by an increase in response to painful stimuli in patients taking opioids. This may be confused with disease progression and the prescriber may increase the dose, however, this aggravates the condition and in contrast, the dose should be reduced. It may be difficult for the clinician to differentiate between hyperalgesia and tolerance, however, hyperalgesia is characterised by a more diffuse pain which involves a different part of the body than the original pain. Hyperalgesia may also develop as a result of stopping opioid medication. [74]

As discussed in the previous section, open label studies report that some patients continue to have a good response to opioids for long periods at average dosages that did not exceed 120mg OMEQ per day, meaning that these effects vary between patients [6]. However, studies of the population of patients prescribed opioids outside of clinical trials have identified that a proportion of patients may not be achieving the good outcomes seen in the select group of patients included within the clinical trials.

2.7. Outcomes of opioid therapy measured through observational studies

This section outlines a number of studies that have identified that patients taking opioid medication outside of clinical trials may not be achieving good pain control and accompanied improvements in quality of life.

2.7.1. Cross sectional studies provide evidence that a large proportion of patients taking opioid medicines may not be experiencing good outcomes

A widely cited cross-sectional survey of the general population in Denmark compared the quality of life (measured using the IMMPACT recommended SF-36 quality of life scale) in patients who were taking opioids (n=288) for chronic non-cancer pain (CNCP) with that of patients not taking opioids with CNCP (n=1,678). The authors adjusted for age, gender, use of antidepressant/anxiolytics and bodily pain (excluded from analysis of pain) (defined as none/very mild/mild or moderate/severe/very severe). Opioid usage was significantly associated with reporting of moderate/severe pain adjusted odds ratio (aOR) 8.10 (95%CI 5.32-12.34). However, it is possible that patients with more severe pain were more likely to be prescribed opioids. Moreover, it is not possible to tell from this study if the patient understood whether they were reporting their pain levels before or after taking the opioid. Another problem with this study was that there was no differentiation between patients receiving opioids continuously or intermittently or the dosages received by patients. With regards to other outcomes, patients taking opioids compared to those not taking opioids were more likely to state that they were in poor health (measured by use of the healthcare system in the last 3 months) aOR 1.98 (1.36-2.87) and were less likely to be employed aOR 0.45 (0.31-0.65) [75].

Similar results have also been observed within a 2007 American cross-sectional random telephone study (Kansas state) in which adult opioid users were found to be unadjusted OR 3.5 (95% CI 2.4-5.3) times more likely to rate their health as poor, to have activity limitations and less physical activity and to have 14 or more days poor mental health per month than those with chronic pain alone. [76]

2.7.2. Cohort studies provide further evidence that patients taking opioids do not achieve good outcomes

Cross sectional studies have the limitation that they measure the relationship between outcomes and opioid treatment at only one point in time. Cohort studies measure outcomes over time and so can show changes in the outcomes as opioid use continues.

A few cohort studies have looked at outcomes as a result of treatment with opioids. An American cohort study of post-menopausal women (50-79 years) (n=1581 receiving opioids out of 67,963 patients in the study) with recurrent pain (low back pain, neck pain, headaches, joint pain or stiffness) found that opioid use (self-reported for 2 weeks or more) recorded at a baseline interview and 3 years later was associated with worsening of pain and physical function (measured using physical domain of the SF-36) 3 years later. This was after adjusting for many factors including baseline pain. The adjusted odds ratio of patient being more likely to be in the "worsening function group" was 1.25; (95%CI 1.04-1.51) [77]. This was a large study in a group of older women, of an age and gender more similar to the types of patients that receive opioids in the U.K. In the study by Foy, 29.9% of patients receiving four of more prescriptions were females aged 65-100 years. This was the group with the largest proportion in comparison 18.1% were aged 50-64 [27]. Thus, in a population of patients that commonly use opioid medicines in the U.K., poorer outcomes are associated with opioid use.

Another study attempted to address the issues associated with cross sectional studies using similar Danish data by comparing self-rated health scores, pain interference with work and ability to carry out moderate activities in the year 2000 or 2005 with the same patient's scores in 2013. The authors stratified results by those who had been newly prescribed long-term opioids in the follow up period and those who had not. The study found that patients taking long term opioid therapy for greater than 3 years were more likely to have decreases in mean values of self-related health (aOR 2.9 (95% CI 1.0-8.2)), pain interference with normal work (aOR 11.4 (95% CI 2.5-51.8)) and impairment of moderate activities (aOR 4.4

(95% CI 1.4-13.4)). This study was limited by the fact that due to the long-term nature of the study patients who did not complete the study would be likely to bias the conclusions, for example patients who died were excluded and so if elderly patients were more likely to benefit from opioid treatment, even if only for short periods, this would be underestimated. Additionally, because mean differences in groups were reported, this may mask the potential that some patients did not experience lower scores after long-term opioids were administered. However, the greatest issue with this study is that only 38 patients were included who had long-term follow up and so the 95% CI for effects were large. [78]

In the U.K., a cohort study [79] evaluated changes in disability over time associated with opioid use (using the Roland Morris Disability Questionnaire (RMDQ)) by following 715 chronic back pain patients for 6 months. This study included patients from 8 GP surgeries from the North Staffordshire and Cheshire area with a mean age of 44 years (max 60yrs), 59% were women, who presented to their GP with back pain. The study used prescribing records to determine opioid exposure. The study found that opioid users, at 6 months, (n=234) were significantly more likely to have higher disability, though this difference was small; adjusted mean difference RMDQ score 1.18 (0.17-2.119). The study adjusted for many confounders including baseline disability. Patients taking higher dosages ≥50mg oral morphine equivalents reported higher usual pain intensities. The authors concluded that, on average, opioids do not allow improvement in function, although some patients may gain benefit. A limitation of this study was the fact that changes in function were not measured before and after opioid treatment was initiated, rather, patients were included if they presented to GP services with back pain within a set time period. Approximately 2/3 of the patients had suffered from back pain for longer than 3 months and it was unknown how long the patients had been receiving opioid medication for. Therefore it is possible they initially received benefits that were maintained over time that this study would not have picked up.

Interestingly, in this study, the researchers found higher levels of distress, fear of movement, catastrophizing behaviours and lower self-efficacy scores to be more common in opioid patients. Another interesting aspect to this study is that NSAID use at baseline was not

associated with disability at follow up, though the authors mentioned this may be because of residual confounding, though may also imply that, in some conditions, patients may continue to take opioids when they are not benefiting from the treatment and this is not as likely in patients using NSAIDs [79]. However, this may be because a prescriber has tried NSAIDs before opioids and the patient continues to take opioid medicines as there is no alternative. Nevertheless, this is still inappropriate if the patient is not benefiting from treatment.

In another U.S.A. based study that questioned 1,229 patients taking long-term opioid medication (120 days or 10 prescriptions in a one year period) at a dosage of ≥50mg OMEQ, 80% continued to receive opioids one year later. Patients reporting more problems with opioids were slightly less likely to continue taking opioids but outcomes such as reduction in pain intensity and increase in function were not associated with a higher probability of continuation. Half of patients stated that they wanted to cut down their opioid consumption. The study results suggested that many patients continued to take opioids despite lack of pain relief and the presence of side effects. [80]

Some of these studies have taken place in North America where opioid prescribing is highly prevalent. However, there are also studies from European countries with funded healthcare systems, where a patient accesses one GP with similarities to the U.K, where opioid consumption per head is similar and even one study conducted within the U.K. and so these studies raise the possibility that there may be patients taking opioids in the U.K. who are not obtaining good outcomes.

All of these studies are limited by confounding by indication, in that patients who receive opioids may have had more painful or disabling conditions and so were prescribed the opioid. As Eriksen [75] notes, many of these patients may have had worse pain and function without the opioid treatment and it is unclear usually whether patients are answering questions based on their pain after they have taken the opioid or when the pain is at its worst. Nevertheless, it is clear that many patients currently taking opioid medication in the community are still in pain with a lack of improvement in function. This means that there may

be other factors that are influencing whether patients continue to receive opioid medication and whether they take high dosages of opioid medication.

2.8. Factors affecting long-term prescribing of opioid medication

Opioids have been found to be likely to be effective, in that they reduce pain scores when evaluated via systematic reviews of short and medium term randomised controlled trials. These trials typically contain only patients from select populations (i.e. excluding patients with comorbid physical and mental health issues). Therefore, we do not know if the benefits in clinical trials are conferred to patients within the community who have different psychological characteristics and potentially different interactions with health care professionals to those within trial situations. However, as is discussed below, chronic pain patients are likely to have these types of comorbidities.

2.8.1. Chronic pain is associated with physical and psychological comorbidities

The link between chronic pain and psychological factors is not restricted to the study of opioid use. In a survey of the U.K. population conducted in 2011 [44], 70% of men and 68% of women with chronic pain of the most severely limiting pain grade (defined as Grade IV severely limiting pain using the Von Korff scale) stated they were moderately-extremely anxious or depressed at the time of survey (measured using the EQ-5D scale). In comparison, within the U.K. population, surveys have shown that 15.7% of people report symptoms of anxiety or depression within the last month, with 8.1% having severe symptoms (symptoms measured using the clinical interview schedule – revised). One third of women (34.5%) and one fifth (20.0%) of men reported that they had ever been diagnosed with a common mental disorder (CMD) (depression or anxiety) by their doctor [81]. Thus, there is a much higher prevalence of depression and anxiety in patients with chronic pain than in the general population.

The link between depression and chronic pain has been shown to be reciprocal in that patients with chronic pain are likely to be depressed and that patients with depression are more likely to have chronic pain. As a patient becomes more depressed so the pain intensity increases and vice versa [82]. When pain and depression co-occur, outcomes for patients in

terms of quality of life, disability and the likelihood of successful treatment are more likely to be poor [83].

It is perhaps intuitive that chronic pain may cause depression, however, the idea that depression may also cause chronic pain is less obvious, yet research has found that this is likely to be possible. It has been suggested that this is due to chronic activation of the hypothalamic pituitary adrenal (HPA) axis due to lifetime stressors, which in turn leads to disturbed function of the HPA axis and abnormal cortisol secretion which can induce cytokines leading to reduced levels of the monoamines serotonin, noradrenaline and dopamine [84].

Chronic activation of the HPA axis has been used to also explain the link between depression, chronic pain and multiple long-term conditions. This can be described in terms of the “allostatic load” model [85]. The idea of “Allostatic load” is a model used to describe the cumulative effect of an individual’s response to lifetime stressors. Within this model, different individuals will have different responses to acute stressors. The body has in place responses that allow an individual to adapt to acute stress in the environment; for example, if an individual has to get away from a particular situation, an increase in adrenaline enables a fight or flight response. However, where this response is “excessive in terms of the extent of a response, duration or frequency of the response (when there is an increased perception of danger)” this can result in “wear and tear” on the body. An increased allostatic load has been linked to having a number of long-term conditions. [85]

The increased likelihood of pain in these patients [42] means an increased likelihood of prescribing of opioids in patients with a number of comorbidities. As opioids are usually tested in patients without multiple comorbidities, trials may underestimate adverse events associated with opioid use. Increased multimorbidity also makes the management of chronic pain more difficult as treatment possibilities are reduced (e.g. NSAID use with chronic renal impairment) [86] and opioids may be more likely to be used. This is also a problem as adverse events may be more likely in patients with comorbidities, for example, as morphine

metabolites are renally cleared, impaired kidney function may lead to an accumulation of these metabolites, increasing the effects and prolonging the effects of the drug [23].

2.8.2. Studies that show an association between opioid use and depression

Studies from a number of countries including the U.S.A. [87-89], Norway [90] and the U.K. [27, 91] have identified that long-term prescribing is associated with patient characteristics such as psychological comorbidities and substance misuse issues. However, as discussed below, the U.K. studies have some limitations and the studies in other countries may not be applicable so the link is uncertain.

It may be the case, if depression develops after opioid use, that this association is found because patients are depressed due to long-term pain, which would suggest that the opioid is not preventing the pain or that the opioid is causing the depression [92]. However, studies have found that depression before opioid use even starts may predict long-term prescribing [88, 89] so this cannot explain the full association between opioids and depression. For example, in one U.S. based study, the incident and prevalent long-term opioid use rates were three times higher in patients with a history of depression (coded as having a depression diagnosis in the two years before opioid use started). Patients with a history of depression received opioids for a greater number of days and were prescribed higher dosages [89].

It is also possible that the patient is depressed over the fact that they are in long-term pain and so the prescriber decides to start opioids. However, one U.S.A. based study also showed that depression was associated with prolonged opioid use even after adjusting for levels of pain intensity and function prior to the patient receiving opioids [93], which suggests that this is also not the case. Chronic pain patients in this study had an aOR of 1.95 (1.15-2.72) of continuing opioid use long-term (3 or more prescriptions) compared to those patients without a mood disorder. One commentary on the study by Halbert [93] referred to above, remarks that if a patient is depressed when they start opioid treatment, this should not theoretically mean they continue to use opioids for longer than another chronic pain patient

who is not depressed, as studies have shown that opioids are not more effective in depressed patients than non-depressed patients [94]. However, there is the possibility that the measure of function (Short Form-12 survey) did not capture all the aspects of disability and that confounding still occurred.

In the U.K., prescribers have reported that they are influenced by what they think are the cultural norms associated with what is acceptable opioid prescribing [9]. These norms are likely to be different from the American system which places patient demand as a priority. Also, the structure of the healthcare system (whether a patient usually gets all their prescriptions from one doctor or multiple doctors and whether a patient can choose which doctors to see) may affect the prescription patterns of opioids within a particular country [14] in that patients who want to obtain opioids can move from one doctor to another until they find one willing to prescribe. Studies in the U.K. may be vastly different to studies from other countries that allow patients to move between doctors. Therefore, specific studies in the U.K. or more similar countries may give a better picture how physical and psychological comorbidities interact with the prescription of opioids within this country.

Two studies [27, 91] in the U.K. have shown a weak association with depression and long-term treatment though they have some limitations. Foy [27], in a study of the factors that affect whether a patient is more likely to receive 4 or more prescription in a year, identified a weak association (aOR 1.12 1.03-1.23) between mental health disorders and receiving more than four prescriptions. However, this study only identified whether a patient was coded with a diagnosis of mental illness within a particular year so diagnoses that occurred outside this timeframe would not have been recorded. In addition, prescribers may be less likely to record diagnoses of depression and more likely to record symptoms of depression due to uncertainty of diagnoses, stigma associated with the diagnoses or the fact that depression is recognised as a condition within the quality and outcomes framework which stipulates certain care standards that must be met for these patients [95]. Though the study would be likely to identify patients with perhaps the most severe symptoms at the time of opioid prescription, by only looking for recorded depression diagnoses Read Codes, this may

underestimate the proportion of patients who have depressive symptoms. Indeed in this population, only 3.1% of patients prescribed four or more prescriptions had a diagnosis of depression in comparison to 2.6% with fewer than 4 prescriptions. This is much lower than the self-reported population average of 8.1% of the population having severe symptoms of anxiety or depression [81].

In a second study, Green [91], also identified within a cohort of older patients (aged 50 and over), who were diagnosed with osteoarthritis that they were more likely to receive a greater number of prescriptions if they had a high (8+) score on the hospital anxiety and depression scale. This study only contained a small number of patients (n=39) who received prescriptions for morphine or oxycodone, was within a localised population (which may not reflect the rest of the U.K. prescribing habits) and only concerned patients with osteoarthritis. It is not currently known what proportion of patients who receive opioids do so for conditions other than osteoarthritis. Therefore, the question as to whether patients with depression prior to starting opioids are more likely to continue opioid use in the wider U.K population remains.

2.8.3. High dosage and long-term opioid use

In two U.S.A. based studies which follow patients from their first prescription of opioid medication until a gap in prescriptions, i.e. followed continuous opioid prescribing, one of the factors found to have the most influence on probable continuation of prescribing was whether or not a patient was receiving a high dosage of medication >120mg OMEQ/day [96, 97]. Thus, receiving higher dosages of opioid medication is associated with long-term use. This may be because patients receiving high dosages were more likely to have long-term chronic pain conditions than those receiving lower dosages.

2.9. Factors affecting high dose prescribing

Another marker of potentially inappropriate opioid prescribing may be use of high dose medication. Guidelines from other countries (U.S.A. [98] Canada [99] , including the current U.K. opioid guideline [69]), generally recommend against the use of higher dosages of opioid. This is due to a number of reasons, primarily that the use of higher dosages has not been tested in clinical trials [69, 100] and the fact that higher dosages are associated with significantly increased risks of adverse events associated with opioids, notably with the increased risk of overdose (Section 2.11.4). The dosage which is defined as “higher dose” varies depending on the guideline. Older guidelines tend to have higher maximum recommended dosages (e.g. 200mg OMEQ/day) [98], based on dosages that were found to be effective for most patients in randomised controlled trials, but later guidelines have recommended lower maximum dosages. This is due to the fact recent observational studies have identified a greater risk of overdose over 100mg OMEQ/day (Section 2.11.4). This change also occurred in the U.K., as in the 2010 version of the British Pain Society Guidelines, a maximum of 180mg OMEQ/day was recommended [101]. However, this was reduced to 120mg OMEQ/day in the recent “Opioids Aware” recommendations which were released in 2015 [69].

2.9.1. Outcomes in patients taking high dosages of opioid medication

Patients taking higher dosages (≥50mg OMEQ/day) were found to have lower self-efficacy scores, greater fear of physical activity and higher levels of disability than those taking lower dosages, in the U.K. based study that looked at back pain patients. Of note, only 25 patients in the whole study received opioids at the highest dose ≥50mg OMEQ/day [79]. Several studies have identified that patients using higher dosages are more likely to have higher pain intensities [102, 103], poorer functional outcomes [104], greater levels of clinical depression [102] and more opioid related problems such as increased side effects, greater work interference and wanting to stop [105].

Ballantyne and Stannard, in their editorial in the BMJ in 2016 [10], have noted how high dose opioid therapy may develop through the misapplication of the WHO Pain Ladder principles for the management of cancer pain to chronic pain patients. They outline the case that prescribers who are presented with a patient who is expressing that they are in unbearable pain, follow these guidelines and increase the dosage of medication that a patient is receiving. However, in chronic pain situations, where the role of psychological factors may be a much greater driver of pain intensity than nociceptive inputs, this approach is likely to be unhelpful and once patients reach high dosages, it may be particularly difficult to reduce them back down. [10]

2.9.2. Studies linking depression and high dose prescribing

Studies have linked high dose prescribing to depression in studies from the U.S.A.[106], Australia [107] and Germany [108]. In the U.S.A. based study by Kobus [106] patients with low back pain were divided into groups based on their opioid dosage within a 90 day period. One group contained patients who received more than 100mg OMEQ/day and the other, less than 100mg OMEQ/day. Male gender (aOR 1.68, 1.37-2.06) (adjusted for age and sex, other variables were included in the model but with no effect), having any of 1 in 4 mental health diagnoses (aOR 1.58, 1.28-1.95), co-prescription of sedative hypnotics (aOR 1.75, 1.42-2.16) or a pain clinic visit (aOR 2.30, 1.80-2.94) was found to be associated with receiving a higher dose of opioid medication. Around 60% of the patients within the higher dose opioid group were prescribed a sedative hypnotic within 6 months of their initial clinic visit. In contrast, another study in the U.S. veteran population which included patients with consecutive pain scores of ≥4 on the numeric rating scale, compared patients receiving ≥180mg OMEQ/day and those dosages <180mg OMEQ/day. Patient factors associated with high dose use included certain types of pain (neuropathy, low back pain) and nicotine dependence [109]. In this study 60.6% of the traditional dose group were depressed compared to 66.9% in the high dose group. Thus, in this study, a relationship between mental health diagnosis and high dose was not identified in the adjusted analysis. However,

the proportion of all patients receiving opioids who were depressed was on the whole quite high [109].

In the Australian study patients were compared in groups of those who were depressed and those who were not (depression was based on patient report). Patients in the depressed group had a median dosage of 73.2mg OMEQ/day (IQR 35.8-150mg) whilst patients without depression had a median dosage of 58.6mg OMEQ/day (IQR 25-102.9mg) [107]. In another paper that concerned the same cohort of patients, one of the greatest differences between the depressed and non-depressed groups was age, with younger patients (19-54 years) being found to have greater pain intensity, more mental health issues and poorer coping styles than the age group over 65 [110]. However, the opioids prescribed to patients within the various age categories varied, with a greater proportion of older patients being prescribed opioid drugs with preparations available which are designed to deliver lower dosages. For example patients in the working age group were more likely to be prescribed oxycodone than patients in the retirement age group. Patients in the working age group were less likely to be prescribed buprenorphine than those in the retirement age group. As the study involved patients that were interviewed, older patients may be less likely to report that they are depressed. Most crucially, as the study involved patients being interviewed for 1-1.5 hours it may have been more inconvenient for working age patients who were actually working (and hence potentially benefiting from the treatment) to take part in the study and potentially led to a biased sample. Also, this study did not use multivariate analysis to explore the link between opioid use and psychological factors so there is the potential that this relationship is due to confounding [110] .

In the German study, which did adjust for a number of confounders including age [108], age was only very slightly associated with high dose use ≥100mg OMEQ/day (aOR 0.98, 0.97-0.99) whilst high dose was found to be associated with depression (both before and after opioid treatment starts) (aOR 1.23, 1.10-1.39). Other variables found to be significantly associated with high dose use included gender (aOR 0.88, 0.77-0.99), chronic pain disease coded (aOR 2.14, 1.90-2.40), somatoform pain disorder coded (aOR 1.35, 1.20-1.53),

hyperlipidaemia (aOR 0.80, 0.71-0.90) low back pain (aOR 0.81, 0.72-0.91) and receiving any anticonvulsant medication (aOR 1.36, 1.13-1.64). [108]

Thus, a range of studies have identified that depression may be associated with high dose opioid medication. There are currently no studies that look at the factors associated with high dose prescribing in the U.K.. However, there are studies that look at factors associated with the receipt of strong opioids.

2.9.3. U.K. based studies that examine characteristics associated with strong opioid prescribing

Foy found that the characteristics most likely (aOR of greater than 3) to be associated with prescribing of strong opioids were increasing polypharmacy and referral to specialist pain management [27], and to a lesser extent (aOR 1-2), being an older female (aged 50-64 years and 65+ years) and being a younger male (18-49 years), having a mental health problem, a definitive diagnosis, having 13 or more consultations, increasing missed appointments and referral to neurology. Even though the authors looked at practice factors (list size, number of GPs, proportion of salaried GPs, practice index of multiple deprivation, patients per GP, training status of GPs and total QOF points), this was not found to be associated with an increased probability of receiving strong opioid medication [27].

Another study, conducted using prescribing data extracted from GP records in the Tayside Region of Scotland in 2010 [28], looked at the factors associated with strong opioid prescribing. This study was distinct from the Foy paper in that this paper included tramadol as a strong opioid and that buprenorphine was only prescribed to less than 0.06% of the population whereas 0.75% of patients received morphine, oxycodone or fentanyl (Zin [2] found that the second most commonly prescribed strong opioid was buprenorphine). In this study, after adjustment, the factors significantly associated with being prescribed a strong opioid were age, gender (female aOR 1.44, 1.38-1.50), increased deprivation (lowest quintile aOR 1.63, 1.52-1.75) and residence (being in a care home aOR 1.25, 1.10-1.42). Death from malignancy in the next 6 months (aOR 6.43, 5.26-7.87) or having 15 or more prescriptions

for other medications (aOR 20.7, 18.9-22.6), had a huge association with a prescription of a strong opioid. Before adjustment, this study showed that older patients had a greater risk of being prescribed a strong opioid. However, after adjustment, this study showed the middle aged (45-64 years) were more likely to be prescribed a strong opioid (uOR 1.64, 1.56-1.74) 45-64 years versus 20-44 years. Thus, the main similarity between the two studies is the strong association between polypharmacy and whilst the Ruscitto study found an association with deprivation and prescribing, the Foy study did not. However, the Foy study was able to adjust for many other factors, including recent mental health diagnosis, and so this is potentially a moderating factor between deprivation and strong opioid prescribing.

Although both studies examine whether patients are stepped up to strong opioid medication, the dosages used by patients were not actually measured. Patients using “strong” opioid medication can be prescribed a range of dosages. The lowest modified release morphine preparation contains 5mg of morphine twice daily whilst the lowest buprenorphine patch is designed to deliver 12mg OMEQ/day. (Contrast this with the maximum dosage of codeine 24mg OMEQ/day and the maximum dosage of tramadol is usually 40-80mg OMEQ/day). [23]

2.9.4. The interaction of opioids in the relationship between depression, the use of opioids and chronic pain

As discussed in the previous section, patients with chronic pain are more likely to be depressed and have multiple physical co-morbidities. Unless patients are carefully selected for opioid treatment then typical chronic pain patients will become typical opioid patients. The problem with this, where opioids are concerned, is that in some patients, conditions such as depression may prolong the use of opioids or increase the use of high dose opioids for a number of potential reasons. As previously mentioned (Section 2.8.1), depression exacerbates pain and it has been suggested that depressed patients may feel greater pain intensities, may experience a greater drive for pain relief [111] and so seek dosage increases. In a study that measured likelihood of opioid misuse, depressed patients were

found to be more likely to use higher dosages than prescribed and to be using opioids to aid sleep. They did not, however, exhibit other symptoms of drug misuse such as borrowing medication [112]. This could have been in an attempt to manage pain rather than for the euphoric effects. Howe and Sullivan suggest that in some cases, opioids may be used as the "only and defacto psychiatric treatment for those in chronic pain" and that depressed patients are more likely to be treated with opioids in the absence of other alternatives, as they show greater pain symptoms and repeatedly search for treatments [13].

Another reason that has been suggested is that patients may use opioids to blunt unpleasant emotions in that "patient start using opioids to alleviate pain. They keep using them to get through the day" [113]. Depression has been shown to be a risk factor for addiction in chronic pain patients [114, 115]. Addiction (defined as compulsive drug seeking) is very difficult to define in this group of patients as it involves judging the intent of a patient's actions as to whether they are seeking opioids for pain relief or for another reason, which the patient may not know themselves.

Depressed patients may also continue to take opioids because they have specific psychological traits (e.g. lack of self-efficacy, catastrophizing) meaning that it is potentially more difficult for them to deal with a difficult situation such as withdrawal, especially if there is no other course of action available. It has been identified in one study that the biggest predictor of continued opioid use was whether a patient thought it was likely they would continue opioid use. Patients who reported it was extremely likely that they were to continue to receive opioids (aOR 4.05, 2.59-6.31) were more likely to continue than those who thought it was unlikely [116].

In both a U.K. [8] and U.S. based study [117], patients have expressed the concern that if they were not receiving opioid treatment, they do not know what alternatives would be available to them. As strong opioid treatments are not usually used first line in the U.K., then it is likely that patients and prescribers have utilised other treatment options that are

available to them first, especially in the case of stronger opioid use. Therefore, they may be reluctant to stop taking medication if they perceive that the opioid is helping to any extent.

In the U.S.A., the term “adverse selection” has been used to describe how some patients may continue to receive opioid medicines for reasons other than good pain relief [12].

2.9.5. Dependence may make it difficult to stop high dose use

Dependence is “the state of habitual use that will result in a withdrawal syndrome upon withdrawal of the drug” [50]. Physical dependence leads to extremely unpleasant symptoms including diarrhoea, rhinorrhoea, agitation, difficulty sleeping, muscle pains, stomach cramps, piloerection and rapid heart rate on cessation of opioid treatment. Psychological symptoms include anhedonia, dysphoria and craving.[118]

Patients taking opioids fear withdrawal and may think that doctors underestimate unpleasantness of withdrawal [117]. Withdrawal symptoms vary between patients, with some experiencing no withdrawal symptoms whilst in some patients, withdrawal symptoms can induce craving and addiction, a clinical situation that can be difficult to manage and which can last for several months past the acute withdrawal phase [119]. This is more likely to occur in patients taking long-term opioid therapy. Though continued use of opioids may lead to a reduction in effect, each dose may still provide relief to the patient and so propagate continued use. In some patients, this can lead to misuse and addiction. However, if a patient continues to receive opioids from their prescriber, this may not be the case. Problems may only arise when a prescriber wants the patient to reduce their opioid consumption, whereby they may continue to seek opioids at higher dosages or eventually, against the recommendations of their prescriber. This can, in some cases, be judged to be a sign of drug misuse and even addiction [71].

Patients may mistake withdrawal symptoms with an increase in pain from the original pain condition and so this means patients continue to take opioid medication as they believe it is helping their pain [71]. Manhapra and Ballantyne, in a recent paper, suggest that patients

may need intense support during this period, to treat the condition once a patient begins to reduce their dosages. They also state that patients often have little insight into their current condition. This means prescribers need training to be able to discuss this topic with patients [71]. A further problem is that there is a lack of evidence of how best to reduce opioid consumption, though a recent systematic review found very weak evidence to suggest that patients may have an improved pain function and quality of life after doing so [117].

2.10. Chronic pain treatment in the U.K.

There are some features of the U.K. healthcare system and the current opioid utilisation factors that may protect the population against the harms seen in the U.S.A. For example, the preferred use of lower potency opioids (codeine rather than oxycodone), having one GP which means that patients are less able to “doctor shop”, the apparent lack of diversion of prescribed opioids for recreational usage and more ready access to substance abuse treatments which may mitigate this risk [14]. However, there are some features of the U.K. healthcare system that could potentially contribute to inappropriate use of long-term and high dose opioids. In the U.K., patients can potentially continue to use opioids “legitimately” for chronic pain for long periods and at high dosages when this may not represent optimal treatment for them. This may be due to the fact chronic pain may not be optimally managed in the U.K. because of the reasons outlined below.

Primary care doctors struggle to manage patients with chronic pain and patients with chronic pain who receive opioids. A study of English GP attitudes, which is almost 10 years old, reported that 80% of general practitioners (n=115) surveyed reported that they thought undergraduate and/or postgraduate training in chronic pain was inadequate [120]. This study also found that young male prescribers were more likely to prescribe opioids. As a result, the characteristics of the prescriber may determine whether a patient receives opioids or not rather than the clinical presentation. Though this study is old, the report of the British Pain Summit, held in 2011 [121] also highlighted that lack of training was problematic, in that training in the field of chronic pain is weak at both undergraduate and postgraduate levels for almost all health care professionals, this report was based on expert opinion from discussion at the meeting. However, studies have been conducted that involve an analysis of undergraduate medical curriculums and identified that undergraduate doctors had a mean of only 12 hours of training regarding pain management [122]. Prescribers also have worries about the long-term management of patients who receive opioids, highlighting the fact that they recognise there are difficulties with repeat prescribing, managing dosages and managing potential addiction [123]. These are areas which may be targeted by additional

training or for procedures to be put in place to help with the management of these patients by a practice [124].

Potentially, as a result of this lack of training, in a qualitative study of opioid use in Leeds by McCrorie, [8] a number of problems were highlighted that could provide clues as to the potential nature of problematic opioid use in the U.K.. Researchers in the study interviewed 15 GPs and 23 patients from the Leeds and Bradford area. Though this was a small sample of GPs, and it may be possible that the sample was biased, the study highlighted how problems with opioid use potentially occur and provides crucial insight into how problems with opioids occur. In a key study in the U.S.A., Von Korff [125] introduced the idea that patients become “de facto” long-term opioid patients; most patients will stop opioid treatment due to adverse effects and lack of analgesia. However, some will continue to use opioids by default as prescribers continue treatment without an adequate management plan and so repeat prescribing just continues, driven by the patient. Importantly, the McCrorie study identified that this could potentially be happening in the U.K. as a lack of shared management plans was identified as a key problem. [8] Patients in this study provided examples of where problems were occurring: (i) one patient (37 year old female) was on 300mcg fentanyl patch (720 OMEQ per day) and stated they thought the GP had not realised that “she had gotten me up to that” (ii) a patient discussed how a GP had said he had given her “everything” so she was questioning why he was reducing her opioids (iii) a GP who didn’t want to bring patient for review because of the impact this would have on other colleagues by blocking appointments (iv) a lack of confidence in pain specialists on the part of patients and GPs and the view that they only prescribed more medication. The study also identified that if a patient is on multiple medications, opioid use may not be prioritised during a medication review because the patient has many other problems.[8]

Song et al [124] conducted a review of strong opioid prescribing in one General Practice surgery in England. They identified that most patients (4 out of 5) received a review within 12 months. However, patients were more likely to have a review if they were older (due to the number of repeat medications triggering a medication review) but not if they were exposed to

high risk prescribing e.g. a high dose of opioid or co-prescription with a benzodiazepine. Within this study, the researchers were unable to identify what occurred as part of the medication review from GP records, highlighting that management plans with regards to pain relief are not documented. An obvious limitation of this study is that it was conducted in only one surgery and that documentation and protocols for repeat prescriptions (i.e. how patients are prioritised for review) vary between surgeries [126]. The opioids aware [69] campaign produced by the Faculty of Pain Medicine part of the Royal College of Anaesthetists, recommends for opioids to be prescribed appropriately; they need to be used as part of a "broader plan including non-medication treatment and self-management" and also "a very detailed assessment of the many emotional influences on their pain experience". To deal with the emotional influences on a patient, patients need access to good quality chronic pain services. The latest commissioning document advising on the commissioning of chronic pain services identified that almost a third of clinical commissioning groups (CCGs) did not commission a chronic pain service, thus in these CCGs, patients may not even have access to a chronic pain service [127].

The pain service must also provide good quality care. To understand the quality of pain services provided in the England, the British Pain Society commissioned a report into the quality of pain services in England and Wales 2010-2011 which identified a number of potential problems with the current service.[128] A problem identified with English pain services include the variability in staffing with only 40% of clinics reporting they employed a psychologist, a physiotherapist and a physician (though 45% of pain clinics did not report what their multidisciplinary staffing was and it may be the case that only those who were concerned took the time to report staffing levels). Only 48% of English services (60% of Welsh clinics) reported they had a clinical psychologist, whilst 29% did not employ a consultant and only 10% of clinics in Wales did not have a consultant. A workforce planning analysis by the faculty of pain medicine has also identified that there are not enough pain specialists to meet demand.[129] In the accompanying patient survey, "very few" patients (3%) had seen a psychologist even after 6 months, though half of patients reported they

were anxious or depressed at referral. In comparison, 56% of patients received new medication.[128] In the Leeds/ Bradford qualitative study of the use of opioids, one GP expressed doubt as to the effectiveness of pain clinics "…every time I send somebody to chronic pain [clinic] they come out with more medication, or injections."[8]

Table 2 National Institute for Health and Care Excellence (NICE) guidelines for the use of opioids

NICE Guideline	Title	Date	Recommendations
Neuropathic pain in adults	CG96[130]	2010	as below
	CG173[131]	2013	only tramadol to be prescribed for acute treatment without referral
Osteoarthritis	CG59[132]	2008	as below
	CG177[133]	2014	If paracetamol or topical NSAIDs are insufficient for pain relief for people with osteoarthritis, then the addition of opioid analgesics should be considered. Risks and benefits should be considered, particularly in older people
Rheumatoid arthritis	CG79[134]	2009	Offer analgesics (for example, paracetamol, codeine or compound analgesics) to people with RA whose pain control is not adequate, to potentially reduce their need for long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase-2 (COX-2) inhibitors.
Low back pain	CG88[135]	2009	When paracetamol alone provides insufficient pain relief offer NSAIDs an/or weak opioids. Consider offering strong opioids for short-term use to people in severe pain. Consider referral for specialist assessment for people who may require prolonged use of opioids.
	NG59[136]	2016	Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective Do not routinely offer opioids for managing acute low back pain Do not offer opioids for managing chronic low back pain

U.K. guidelines (for National Institute for Health and Care Excellence guidelines see Table 2) generally recommend that opioids are prescribed (or not) but do not provide details

regarding recommended dosages. Guidelines have also been a source of confusion as the recommendations of strong opioids for chronic back pain changed from recommendations to prescribe to the recommendation that they are initiated only by a specialist [136].

In the medical media, a number of UK based clinician commentators have stated that there may be problematic use of opioids in the U.K. in that patients may be receiving opioids at doses that are “too high for too long” [7], that GPs are prescribing opioids too liberally, that prescribing opioids is common practice [137] and that current services for addiction are not suited to patients with chronic pain [138]. There have also been calls by key clinicians that patients with chronic pain who take opioids should have medication reviews at least annually.[139] Therefore, the management of chronic pain in the U.K. may not be optimal and this could possibly lead to long-term and high dose prescribing of opioids.

2.11. Adverse events that have been associated with opioid medicine use

Opioid therapy is not without risks and adverse events associated with opioid therapy can impact on quality of life. Continued use of opioid medication is associated with adverse events that are only becoming apparent in recent observational studies.

2.11.1. Short- term adverse events

The six most common adverse events reported within short term RCTs of opioid use include constipation (16%), nausea (15%), dizziness/vertigo (8%), somnolence/drowsiness (9%), vomiting (5%) and itching (4%) [140]. When strong opioids are considered, the prevalence of these side effects increases, the most common still being constipation (41%) [141].

2.11.2. Long-term adverse events

2.11.2.1. Opioid induced bowel dysfunction

Opioids act on the intestinal musculature by binding to MOR receptors in the gastrointestinal tract. Here, they cause reduced propulsive intestinal movements, decreased intestinal secretions (with enhanced reabsorption due to slower transit times) and increase in non-propulsive segmental muscle tone [142]. This results in hard stools, a feeling of incomplete evacuation, straining, abdominal bloating and distension with pain and gastro-intestinal reflux [143] These symptoms may develop into more serious problems, including faecal impaction, bowel obstruction, incomplete drug absorption, urinary retention, and delirium [144].

Although other short term side effects such as nausea and vomiting may reduce with long-term use, constipation does not tend to subside. Exogenous opioids may cause bowel dysfunction (less than 3 bowel movements per week) in around 40% of opioid users [141, 145] and is unlikely to improve throughout the period of treatment with opioids [69]. An internet based study of 322 patients found that in those who were taking opioids, a third of patients reduced, stopped or missed their opioid medication in order to ease constipation [143]. Another internet based survey which involved 359 opioid patients with opioid induced constipation found it to be associated with a significant reduction in quality of life scores

(Short Form-8 (SF-8)) and increased visits to primary care compared with non-opioid treated patients[146].

2.11.2.2. Endocrine effects

Opioids may alter endocrine function by binding to opioid receptors in the hypothalalmus and inhibit secretion of gonadotrophin releasing hormone (GnRH). This in turn disrupts and reduces luteinising hormone (LH) and follicular stimulating hormone (FSH) release from the anterior pituitary [147]. Opioids also act directly on the testes in men, reducing testosterone production and the ovaries in women reducing estradiol release. In men, this may cause erectile dysfunction, weight gain and decreased energy. In both sexes, reduced libido and infertility may occur [147]. A recent systematic review included studies that looked at hormonal changes in women aged 18-55 years. The review reported that there was weak evidence that long-term opioids cause reproductive side effects in women of this age, and suggested that amenorrhoea and decreased libido could occur as a result of opioid treatment but that further studies in larger populations were needed to confirm this association [148].

2.11.2.3. Immune effects

Opioid receptors are present on the surfaces of immune cells and prolonged exposure to opioids depresses immune function [149]. Opioids have been shown invivo to affect various immunological processes including the production of antibodies, T cell activity, cytokine expression and phagocytic processes [150], though the clinical implications of these is unclear[151]. One large observational study (case control) using medical records which looked at the risk of pneumonia in older adults (n=1,039 cases, n=2,022 controls) (>65) found a slight overall increased risk (OR 1.38, (95%CI; 1.08, 1.76)) for opioid users versus non-opioid users. This risk was greatest in the first 14 days (OR 3.24 (95%CI; 1.64, 6.39)) and higher in patients using longer acting opioids (OR 3.43 (95%CI; 1.44, 8.21)) versus shorter (OR 1.27 (95%CI; 0.98, 1.64)). No association was observed between increased dose and increased risk of pneumonia [152].

2.11.2.4. Risk of fracture

An increased risk of fracture has been associated with patients using opioid medication. A systematic review of cohort studies (n=8), with six assessed to be of good quality (using the Newcastle-Ottawa scale to assess quality) identified that opioid use was associated with a pooled relative risk of 1.88 times (1.51-2.34) [153]. However, it is possible that patients are receiving opioids medications to treat conditions that would increase their risk of falling or fracture. Two different potential mechanisms have been suggested for this association. Firstly, these medications may induce falls due to dizziness and sedation and secondly, due to the endocrine effects that may lead to androgen deficiency and osteoporosis [154]. A study using data from the Clinical Practice Research Datalink in the UK found that the risk of fracture was greatest in patients who used higher doses but that this risk decreased rapidly with increasing use (greater than one prescription). The authors reported that this result favoured the possibility that initial central nervous system effects may be the cause of the increased risk [154]. However, it is possible that in some cases, an opioid may be prescribed to treat a fracture and a delay in the administrative process may mean that it appears that the opioid was the reason for the opioid to be prescribed or that an acute condition for which the opioid was prescribed increased the likelihood of a fall or fracture. This would mean that an association would be found but that it was not the opioids that increased the risk of fracture.

2.11.3. Addiction

In addition to concerns that clinicians may have over mortality and morbidity, one of the main apprehensions patients have about taking opioids is the fear of addiction [155].

Addiction in chronic pain patients is hard to define as traditional methods of defining addiction may not be applicable to patients taking opioids for chronic pain [73]. For example, withdrawal and tolerance were previously used to define addiction (DSM IV) whereas it is now recognised that many chronic pain patients will have experienced these phenomena whilst taking their medications as prescribed. A systematic review has attempted to report

the prevalence of addiction defined addiction in terms of three different types of behaviours determined by a consensus panel of experts, (1) drug misuse defined as “opioid use contrary to the directed or prescribed pattern of use regardless of the presence or absence of harm or adverse effects”, (2) Abuse : Intentional use of opioid for a non-medical purpose such as euphoria or altering one’s state of consciousness (3) Addiction: Pattern of continued use with experience of, or demonstrated potential for harm, (e.g. “impaired control over drug use, compulsive use, continued use despite harm and craving) The results of the systematic review identified a huge range in probabilities of drug misuse and addiction (only one study identified the risk of abuse). The range for misuse was 0.08-81% whilst the range for addiction was 0.7-34.1%. As there was such a discrepancy, the authors calculated weighted means and found that misuse occurred in 21.7-29.3% of patients and addiction occurred in 7.8-11.7%.[156]

2.11.4. Mortality associated with Opioid Use

Opioids predominately cause death in acute use by respiratory depression. Opioids acting within the brain stem reduce respiratory rate and tidal volume [157]. Opioid users are particularly at risk when starting therapy (due to the risk of the initial dose being too high), when doses are titrated (if they are titrated too quickly) and if opioids are used with other drugs that potentiate their respiratory effects (e.g. benzodiazepines)[158].

The rise in opioid prescribing first gained publicity in North America, a country which has been catastrophically affected by opioid usage. In 2015, 33,091 people [159] died of opioid overdose (data includes overdoses attributed to prescription and illicit use of opioids) and overdose is the leading cause of death in Americans under the age of 50. In 2015, the equivalence of 62 people died every day due to overdose. Death rates vary widely between states, a finding partially attributed to the varying volumes of opioid prescribed per state [160]. The highest death rate from opioid use in 2015 was (illicit and prescribed) 41.5 per 100,000 population in West Virginia, compared to 6.9 per 100,000 in Nebraska [159].In comparison, other countries such as Canada experienced 7.9 per 100,000 apparent opioid

related deaths in 2016 (though death rates per state vary widely in Canada also)[161] In England and Wales, the death rate due to opioid related overdose deaths was 3.49/100,000 [162]. Therefore, not as many people in England and Wales are currently dying from opioid overdose as in North America and Canada.

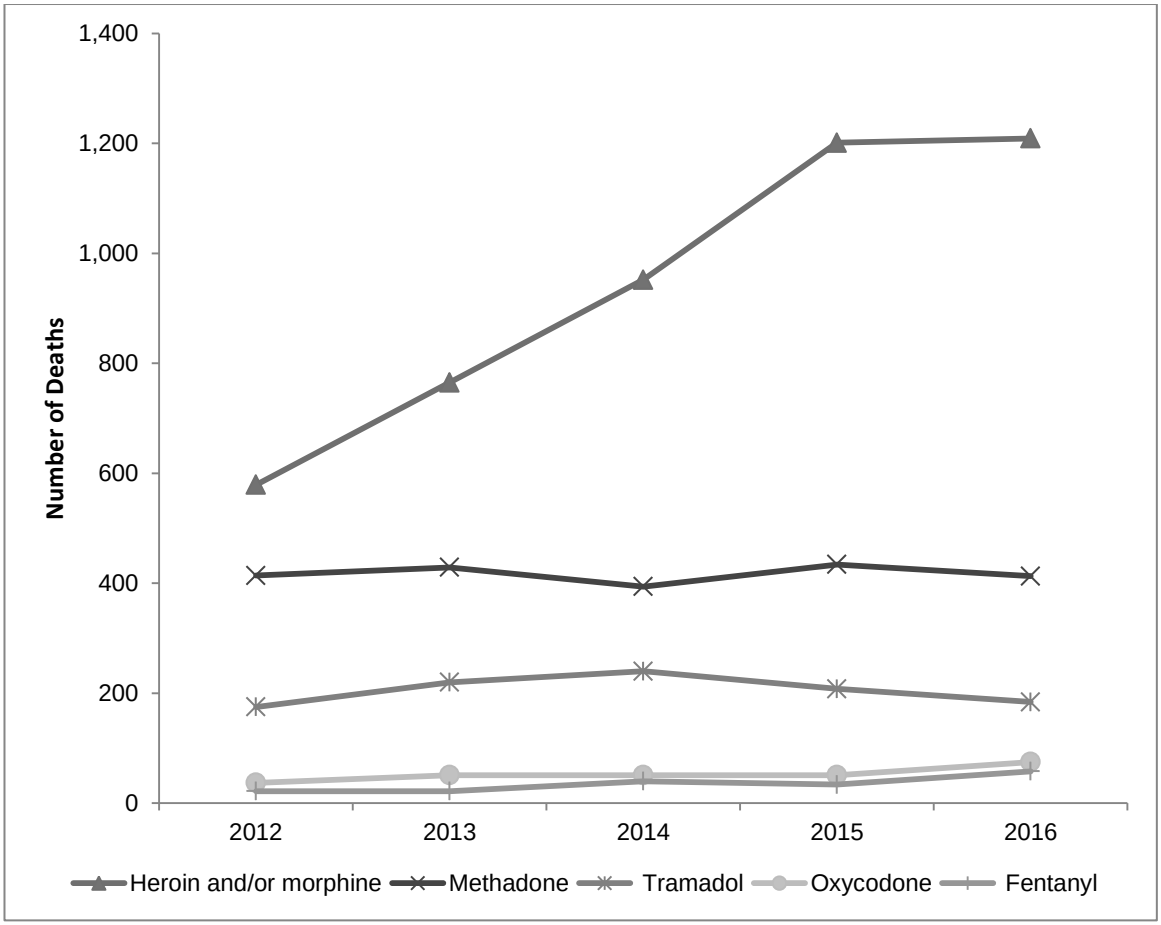
Risks of overdose and overdose death from prescription opioids have been linked to average daily dose within observational studies in both Canada and the U.S.A. A Washington State based study that analysed prescribing data and overdose rates in 9,940 patients taking opioids for CNCP found that the rates of overdose increased with higher doses. The total number of overdoses was 51 including 6 deaths. An overdose rate of 0.2% was found in patients using doses between 1-20mg/day morphine equivalents dispensed, 0.7% in patients using 50-99mg/day and 1.8% in patients over 100mg/day (an 8.9 fold increase 95%CI; 4.0, 19.7) [163]. Though this was a small sample with a small number of overdoses, these results have been replicated elsewhere. A case cohort study using veteran healthcare data (n=154,684 controls, n=750 cases) calculated hazard ratios comparing data from patients prescribed 1 to 20mg/day morphine equivalents with patients prescribed over 100mg/day. For chronic pain patients, there was a seven times increased risk of overdose in the higher dose band [164]. In comparison, a Canadian case control study found a 3 fold increase in risk of death when patients were prescribed doses greater than 200mg morphine equivalents compared with risk of death in patients prescribed doses less than 20mg[165].

In England and Wales, an increase in opioid related deaths has been recorded but the rise is not nearly as dramatic as within the U.S.A. There has been a rise in heroin/morphine related deaths in the past five years [162] After increasing in recent years, tramadol deaths reduced in 2015 [37]. Most worrying, in later years there has been a rise in deaths due to fentanyl and oxycodone (Figure 2) [162].

Further information on the nature of deaths linked to psycho active substances is provided by coroners to the national programme on substance abuse deaths (NPSAD). Of the 1,237 deaths in England in which psychoactive drugs were implicated, in 2013 77 included “other

opioids (not heroin/morphine or methadone)" as the sole cause alone. An additional 380 (30.7%) deaths included "other opioids" as a contributing drug, 169 (13.7%) of these deaths included codeine in combination and 126 (10.2%) tramadol in combination with other opioids. Many of the deaths from "other opioids" included other substances. These were most likely to be alcohol, antidepressants, heroin/morphine or hypnotics/ sedatives. Thus, though the number of people dying from heroin/morphine use (40.8% of deaths implicated in combination with other drugs) is dominated by illicit use (only 7.1% were thought to have been prescribed heroin/morphine), a large proportion of deaths are due to other opioids usually in combination with other drugs (though only 29.8% had been prescribed these drugs). [166]

Figure 2 Number of drug related deaths in England and Wales attributed to opioid poisoning ONS 2012-2016 [162]



2.12. Opioids and benzodiazepine combination use

2.12.1. Increased likelihood of overdose when opioids are prescribed with benzodiazepines

An increased risk of overdose and death is seen when patients receive benzodiazepines concomitantly with opioids. In a recent study [167], concomitant opioid and benzodiazepine prescribing, in privately insured patients in the U.S.A., defined as prescriptions that over lapped for at least one day, was associated with an increased risk of emergency room attendance or inpatient admission for opioid related overdose, aOR 2.14 (2.05-2.24). One limitation of this study was that this only included patients who did not die and presented at emergency departments for treatment. This may well mean that the study underestimated the proportion of patients who experienced an overdose [167]. Also from the U.S.A., in a population of Medicaid patients, a study identified that concurrent sedative hypnotic use was associated with faster time to fatal opioid overdose aHR 6.4 (5.0-8.4). Of particular concern was the fact that a faster rate of overdose related death (aHR 5.6 1.6-19.3) was found in patients who were receiving lower dosages (1-19mg/d) of opioids in combination with benzodiazepines [168]. A further study in the U.S.A. found that the rate of overdose related death was ten times greater in patients who were dispensed both opioids and benzodiazepines at the same time [169].

In England, 24.7% (n=306) of all drug deaths recorded in 2013 included a hypnotic/sedative used in combination with another drug (only 19 deaths occurred in which hypnotic sedative drugs were implicated alone); of these 125 (40.8%) included an “other opioid” as a contributing drug, 109 (n=35.6%) patients had methadone as a contributing drug, whilst 153 deaths (50.0%) had heroin/morphine as a contributing drug [166]. These figures show that a high proportion of patients in the U.K. that are dying from hypnotic/sedative medication were also consuming opioid drugs.

2.12.2. Benzodiazepine concurrent use may be being used to treat chronic pain but has been shown to be a marker for addiction

One Norwegian study found that benzodiazepine use by a patient in years prior to opioid use was a predictor of future opioid use, even after adjusting for musculoskeletal pain, alcohol, smoking and SES variables aOR 3.1 (2.1-4.6). Receipt of a benzodiazepine prior to opioid use was a stronger predictor of receiving an opioid than the patient reporting they were in pain before opioid use. The authors suggest that benzodiazepine use could be a proxy for psychiatric disorders which may predict initiation and continuation of opioids [170]. Similarly, a study from the U.S.A. also identified that prior use of benzodiazepine drugs was found in one study to predict long-term opioid use [88]. In this study, of the patients who received prescriptions for a benzodiazepine in the year before long-term opioids use started, 4.5% continued using opioids for at least one year in comparison to 1.8% of patients who did not receive benzodiazepines in the year prior to long-term opioid use. Thus, benzodiazepine use may be a marker for patients who are likely to continue opioid therapy, be it down to certain types of pain condition (for example, back pain) or certain types of patient (for example, patients using benzodiazepines to treat anxiety). Benzodiazepines may be prescribed to treat low back pain. As part of the back pain clinical guideline, NICE recommended that research be conducted as to the clinical and cost effectiveness of benzodiazepines in the management of acute back pain so as yet there is a lack of good quality evidence as to whether benzodiazepines are effective for acute pain. By doing so, NICE recognise that prescribing benzodiazepines for back pain is a common practice [136].

Due to the fact these drugs are also used to treat anxiety and can boost the euphoric effects of opioids, this combination is open to misuse. Additional benzodiazepine use has also been shown to be one of the strongest predictors of opioid misuse in a cohort of Danish patients from a multidisciplinary pain centre who were screened for addiction [171]. Park, using a cohort of patients from the U.S., found that patients who were receiving benzodiazepines were associated with receiving two early refills of opioids adjusted hazard ratio 1.54 (95% CI 1.09-2.18) [172] . Nielsen, in a cohort of Australian chronic pain patients, also identified that

patients receiving opioids and benzodiazepines were more likely to be receiving high dosages of opioid medication, current antidepressant usage, other illicit drug use and have lower self-efficacy scores [173]. Therefore, opioid and benzodiazepine prescribing is a potential marker for misuse.

2.12.3. Patients commonly use combinations of opioids and benzodiazepines in various different countries

The proportion of patients who receive opioids and also prescriptions for benzodiazepines varies between populations. In a group of Swedish patients [174] receiving slow release opioid medication (morphine, hydromorphone, oxycodone, fentanyl, buprenorphine), 22% of patients were recorded as also receiving an anxiolytic benzodiazepine (alprazolam, diazepam, klobazam, lorazepam, oxazepam) as an add on to their first slow release opioid therapy [174].

A study based in Norway [175] used a cohort of persistent strong opioid users (extracted from a database containing all patients who received opioid prescriptions in the country) who had received at least one prescription for an opioid every year for five years starting use in 2005 or 2006 (n=1233). Patients were stratified into groups of patients dependent upon the amount of opioid prescribed in the last year of follow up. Of patients who received high dose opioids (>730 DDD/year equivalent to 50mg OMEQ per day or 240mg/day of codeine), 77% received a benzodiazepine and 52.3% also received >200 DDD of benzodiazepines at the same time.

In Australia [173], one third of patients in the POINT study (33%) reported that they used benzodiazepines in the past month with 17% using benzodiazepines every day. This study recruited patients who had received either morphine, oxycodone, buprenorphine, methadone or hydromorphone (Australian “schedule 8” opioids) opioid medications for at least 6 weeks. Patients who were taking daily benzodiazepine medication and high doses of opioid medication (>200mg OMEQ) were more likely to report less self-efficacy when managing

pain and higher use. Thus, use of opioids and benzodiazepines is common in other countries.

2.12.4. Use of benzodiazepines in patients who are receiving high dosages of opioid

Though there is added risk of taking opioids at high dosages, studies have found that patients are more likely to take benzodiazepines in conjunction with high dose opioids.

Using veterans medication records in the U.S.A. [109], Morasco reported that the probability of receiving a concurrent benzodiazepine and opioid combination increases if a patient is taking high dose (>180mg OMEQ/day) compared to lower dosages of medication; the proportion of patients receiving benzodiazepines in the high dose group was 32% compared with 25% in the lower dose group and 10% in a non-opioid group who also had chronic pain (defined as having a pain score of greater than 4 in at least three months of 2008). Of particular concern was the fact that another study observed that this practice increased over time. In a cohort of 315,428 privately insured patients in the U.S.A, 9% received an opioid with a benzodiazepine in 2001 whilst 17% received the combination in 2013 [167].

However in contrast, in Denmark the proportion of persistent opioid users receiving concomitant benzodiazepine use has decreased. Combined use was measured in the National Danish Health and Morbidity surveys [176] 2000 2005 2010 2013 which also took information from the Danish National Prescription Registry. This study found that the proportion of persistent opioid users (defined as patients who had received an opioid prescription every month for at least six months in the previous year) who also used benzodiazepine medication decreased from 2000-2013. In 2000, 60% of persistent opioid users received opioid medication whilst in the 2013 surveys, 33% of persistent opioid users received any benzodiazepine. This trend was seen in patients using the highest doses of benzodiazepines and the authors say probably reflects the decline in the use of benzodiazepines on the whole within the country. [176]

Thus, it seems in many countries, patients are receiving concomitant opioid therapy, with some countries seeing an increase in co-prescribing of opioids and some a decrease. In an article that discusses whether the U.K. is likely to see the same opioid crisis as the U.S.A., the authors express the belief that as the U.K. has seen a decrease in benzodiazepine prescribing since the 1980s, this combination of medication may be less likely to occur in the U.K. [14] Indeed, a recent study using CPRD has shown that use of benzodiazepines has decreased in the U.K. in the past two decades. The prevalence of benzodiazepine use decreased from 3.5%-2.6% from 2000-2015 [40]. However, whether the use of benzodiazepines in certain populations (such as chronic pain opioid users) is uncommon has not been established in the population as a whole. Therefore, it is important to clarify whether opioid and benzodiazepine use is common in the U.K. to see if this may be an issue for further research or to address through prescribing quality improvements.

2.13. Summary and research questions

Opioid prescribing in general and specifically long-term opioid use is increasing in the U.K. without a reliable evidence base. The “Opioids Aware” initiative recommends that opioid therapy is introduced as a trial with a long-term plan for the management of the chronic pain condition. Various commentaries and qualitative studies identify the possibility that some patients are receiving opioids without this plan in place and that patients may fear stopping (due to withdrawal and no alternatives) even if they are not benefiting from treatment. In other countries (including Norway with a similar health care system and levels of opioid prescribing to the U.K), patients receiving opioids have been found to still be in high levels of pain. Surveys in other countries have identified that many patients want to stop opioid treatment and have a reduced quality of life. Therefore, there is the potential that patients in the U.K. do not receive optimal treatment for their chronic pain.

The use of opioids in the long-term or at high doses has been found in other countries and to some extent in the U.K. to be associated with psychological factors. This may mean that certain factors other than good response to medication affect the likelihood of continued and high dose use. Ballantyne and Sullivan introduced the idea that chronic opioid therapy may perhaps be being used as “comfort care”, with patients being treated, not just for physical pain, but unintentionally for the emotional and psychological elements that accompany long-term pain. They suggest that adverse selection may be occurring in which the riskiest patients self -select for long term treatment with the highest dosages and riskiest regimes.

Opioid use is associated with a high probability of adverse events, which are not insignificant, in that a high proportion of patients may withdraw from RCTs due to their severity. Use of high opioid dosages, especially with additional benzodiazepine prescribing, has been linked to increased risks of addiction and overdose. Aside from this risk, there is the possibility that patients are receiving high dosages due to poor management of chronic pain (possibly due to insufficient access to understaffed multidisciplinary pain care). Discussing reducing patients from high dosages of medication has been described as one of

the “hardest conversations in medicine” [177] whereas GPs have expressed that they feel they are inadequately trained in treating chronic pain. It is important to identify how many of these long-term and high dose users there are in the U.K.. It is also important to identify how long they are taking these dosages for and to see whether there are any indications that opioid treatment may not be optimal in these patients in that they are being prescribed to patients with psychological comorbidities, for long periods or at high dosages, or for long periods at high dosages. Current research in the U.K. has been limited to smaller regional cohorts, did not explore measures of long-term use and used strong opioids as a proxy for high dose use.

Therefore, the aim of this PhD is to describe the prevalence of long-term and high dose use and to describe how different factors influence the use of long-term and high dose opioids.

The objectives are:

- Define a cohort of patients receiving opioids for non-cancer pain
- Determine a definition of long-term use and see how factors relate to discontinuation of patients taking opioid medication
- Determine the dosages of opioid medication patients are prescribed, the regimes they use at various dosages and see how dosage influences long-term use
- Determine how factors are related to whether patients receive high dosages and the characteristics of patients who receive high dose opioids and long-term high dose opioids

It is important that patients and prescribers are aware of the likely length of treatment that a patient is receiving and that processes are put in place that avoid de facto [125] long-term use by defining long-term use. This may help to determine clinical check points at which patients are reviewed. If it is found that there is some evidence of adverse selection, in terms of long-term and high dose use, as we know that this can be associated with poor quality of care, then it is important that further work is conducted at a patient level to see what quality

of care these patients have received and to measure their quality of life whilst taking opioid medication. Future research may also be tailored to certain problematic groups if they are identified.

2.14. Data Source – The Clinical Practice Research Datalink

2.14.1. Overview of the Clinical Practice Research Datalink (CPRD)

The Clinical Practice Research Datalink (CPRD) is a large database of primary care records belonging to patients who receive care from the National Health Service (NHS) within the U.K. The database was created in 1987 [178]. CPRD contains data for approximately 5 million currently registered patients [179]. In the U.K. most patients (98%) are registered with a NHS General Practitioner (GP) who acts as a gate-keeper to further non-emergency treatments and who prescribes the majority of medications. Due to the extensive amount of information contained within CPRD (detailed in Section 2.2.3) CPRD has been used for many studies that examine the use of drugs in “real life” patient populations [178].

2.14.2. Accessing the data

CPRD data can be accessed via a secure website by researchers that have a paid subscription fee.

2.14.3. Creating a list of relevant patients

CPRD contains data for around 8% of the population of the UK, which includes patients with a wide range of conditions and medications. Clinical data is coded via the use of version 2 Read Codes. Typically, a list of patients with certain characteristics (specifically patients prescribed a certain drug or patients with records containing a certain Read code) within a certain time period is created and this list is used to extract all data for each patient of interest. This is so that only data from relevant patients is retrieved for further analysis.

Lists based on drug names

Lists of drugs are created by searching for generic and branded drug names using the online “product code” browser. The product code is a number that is attributed to a particular presentation of a drug e.g. codeine phosphate 15mg tablets (though there may be many different product codes for this same drug type, strength and formulation due to the fact that,

for example, there may be several manufacturers of this presentation type). As an additional check (that all relevant product codes are included) product codes can be identified by BNF chapter.

Lists based on Read codes

Lists of Read codes can be drawn up using a range of methods. For example via searches for strings of text within the Read code description, reviews of the entire code list available or by using published lists that have been validated via contact with a GP practice or other data sources.

2.14.4. Retrieval of data for patients identified via method detailed in 2.14.3 and description of the data extracted

Using a list of the patient identification numbers identified in the primary search for product codes and/or Read codes as a template, all data available for each patient for the entire time they contribute data is downloaded in a number of different files.

For example, the patient file contains demographic information (including age, sex, practice and region). The therapy file contains details of each prescription entered onto the computer. For each prescription the date of issue, name, form, quantity, strength and in some circumstances the dosage is usually present within the data. An algorithm to identify the numerical daily dosage has been developed and identifies the numerical daily dosage (NDD) associated with the dosage wording for 95% of the dosages within CPRD [180]. However, this does mean that some dosage wordings are missing or incomplete. The clinical file contains a list of Read codes entered by practice staff for each patient (other files containing information such as referrals and test results are also available). These codes are used to identify a plethora of clinical events (e.g. diagnoses and symptoms), referrals and tests. Each record in each file contains a patient identifier that is unique to each patient so that data pertaining to each patient can be linked and then used to create exposure and outcome variables.

In addition, CPRD contains other information such as events such as date of death (though this can also be obtained through linkage with ONS data). Health care access is also recorded as number and nature of consultations and referrals. Extra information regarding the patient or practices socioeconomic status can be requested in addition to hospital episode statistics and death dates from the Office of National Statistics, however this is only available for English practices [178]. There are also linkages available to other data sources such as cancer registries. This information also contains the unique patient identifier which can also be used to link this information to the information in the files downloaded from the website. However, linked data is not available for all patients within CPRD; linkages are only available for English practices and only a proportion of English practices have agreed to linkages. This means only 58% of patients within CPRD have linked data. Because of this care should be taken when extrapolating results using the linkage data to the whole UK.

2.14.5. Critique of the use of CPRD

CPRD is a very large dataset with over 5 million active patients in 2009 thus large sample sizes are available that should increase the likelihood of the detection of statistically significant differences between populations where they are present. The data contributed is data from the NHS, which offers cradle to grave care for multiple conditions, which is co-ordinated by a GP. Because of this it has been reported that within CPRD half of patients (currently registered in July 2013) have almost ten years of follow up (9.4 years, interquartile range 3.4-13.9) [178].

Due to the fact prescribers use their computer systems to manage their patients on a day to day basis to prescribe medicines, it is likely that the data relating to opioid use is complete and so will be a reliable record of the medicines prescribed to a particular patient. Patients are selected from all regions of the country and so patterns of opioid prescribing will incorporate the influence of different policies from several areas.

In order to ensure there is a consistent upload of data from each practice (as any absence of data transfer may mean that diagnoses or prescriptions are missed) CPRD monitor expected

numbers of certain events from each practice. One such event is the number of deaths that occur within a particular time period and this is checked to ensure that the expected number of deaths have occurred, if not this is queried with the practice. Each practice is attributed an "up to standard" date at which the data transfer met the minimum standards for data continuity. When defining lists of patients an option can be selected to ensure that they were "acceptable" patients when a code was added or a medication prescribed. This ensures that patients have some measures of data quality for example that they were currently registered at the surgery (i.e. not a temporary patient), and that they had a valid age and gender [178].

Though these processes ensure that data is complete in terms of the data that is extracted from the surgery computer system, whether a health care professional actually enters a Read Code for a particular condition is likely to be much more variable. A GP may enter the details of a patient's condition using free text but this may not actually be coded. The variability between coding depends on the condition that is coded [181]. Therefore although CPRD is a useful data source the reliability of each variable must be considered when conducting studies using this data.

CPRD is representative of the age and sex of the population [178] but, it may not be representative in terms of other demographics for example regional distribution and the size of GP surgeries contributing data [178]. This means that it is possible that certain types of surgery are underrepresented or overrepresented and therefore do not reflect the exact demographic of the U.K. population. If, for example, CPRD is underrepresented in more deprived areas and that opioid prescribing is higher in these areas this would lead to an underestimation of the prevalence of opioid prescribing in the U.K. as a whole. However, comparisons can still be made between different socioeconomic areas within a particular sample of patients.

Surgeries that do not contribute data may be different in some way to those that do contribute data. For example, surgeries that are more likely to contribute data may be those that are happy for their clinical decision making to be scrutinised by many research teams.

Contributing surgeries may also be more likely to be interested in research and so are more likely to keep up to date with the latest research and recommendations. This may influence their practice.

Surgeries that contribute data to CPRD use a particular computer system named “Vision”. The type of computer system used has been linked in past studies to whether a surgery obtains a certain number of points in the Quality and Outcomes framework [182], thus the type of clinical system used by a practice may influence the way they treat their patients. It is possible that the fact that Vision is used in these practises may also influence the way patients are treated in terms of how surgeries organise and manage their repeat dispensing systems which may in turn influence how long patients continue to receive opioid medicines.

In order to use CPRD researchers must submit a protocol to the Independent Scientific Advisory Committee (ISAC) before publishing research, this ensures that the data is only used for studies that are of a minimum standard and patient confidentiality is maintained.

In conclusion, due to the nature and size of CPRD and the fact that the database contains data representative of actual U.K. prescribing practices, the project will use CPRD as a data source. However, when interpreting the results of this thesis, it must be borne in mind that the data may not be representative of the whole population of the U.K..

Chapter 3. Selection and characterisation of a cohort of opioid medicine users from CPRD

3.1. Introduction

In this first results chapter a data source, the Clinical Practice Research Datalink (CPRD) (2.14), was identified, a cohort of opioid medicine users extracted and the suitability of the data from these patients to answer the research questions outlined in Chapter 2 determined. The main reasons for the use of CPRD as the data source were; the large number of patients contributing to the database, the possibility that patients can be followed in the database over long periods of time (to determine whether patients use opioid medicines in the long-term) and the fact that the database contains demographic data (including markers of deprivation in linked practices), prescribing data and diagnostic data (which can be linked to long-term opioid usage). CPRD also has the advantage that the database was designed for research and has inbuilt markers of data quality (2.14).

Patients were selected to be included in the study cohort if they were prescribed an opioid medicine at any point in the year 2009. The start of the study time period for was chosen as 2009 as it allowed for the longest follow up period after the Shipman regulations which were brought into effect in 2006 and also after the full withdrawal of co-proxamol in 2008 which changed the types of opioid medicines prescribed in the U.K.(2.4.1).

Studies using data, from a prescribing database such as CPRD, have the limitation that data can potentially be incomplete because of the fact that patients can still receive prescriptions that are handwritten. This is a particular problem with regards to some scheduled controlled drugs (including most opioids) as in the past there was a legal requirement that these prescriptions were handwritten. However, this changed as a result of the Shipman enquiry. A key recommendation by the enquiry was that prescriptions for controlled drugs were required to be generated via computer after this time, whereas in the past prescribers were required to handwrite the prescriptions to reduce the risk of forgeries. [19] As a result of this recommendation, from this point onwards, it would be less likely that prescriptions would be omitted from the GP electronic records, and therefore CPRD, so the data would likely be more complete. Additionally, as the prescriptions no longer had to be copied onto the GP

computer system, it would be less likely that the data would be entered incorrectly as the data was no longer transcribed. Also as a result of the Shipman Enquiry, prescriptions were limited to thirty days in length. This is likely to influence the persistence (the length of time a patient continues to take the medicine), in that the prescriber may be required to generate the prescription more often and potentially review the patient more frequently.

Another consideration is the length of follow up of patients as this thesis aims to look at long-term prescribing of opioid medicines. The extraction of data from CPRD took place in January 2015 and so the maximum possible time a patient could contribute data was 6 years. Previous studies have evaluated opioid usage up to a maximum follow up time of five years [96] and so this length of time is comparable to the length of previous studies.

Although CPRD is representative of age and sex of the population (2.14) it is possible that the prescribers contributing to the data prescribe different types of opioid medicines. Therefore in this Chapter the types of opioid medicine drugs used were compared to English dispensing data (as the majority, 76.1%, of surgeries that contribute data are within England and surgeries with linked data are only in England). This was to identify any differences in prescribing compared to the population and to determine whether results can be generalised to the population. The prevalence of opioid medicine use in the U.K. population is also calculated. This chapter also includes data on the characteristics of the cohort so this can be compared to future studies and to aid understanding of the results of the thesis.

In this chapter, the patients receiving prescriptions of opioid medicines are divided into two groups, new users and existing users of opioid medicines. This is to provide a better impression of the characteristics of those patients who have just started receiving prescriptions for opioid medicines compared to those who have been receiving prescriptions for some time prior to 2009. The number of physical and psychological comorbidities are compared in new and existing opioid medicine users to evaluate whether there is any evidence of adverse selection in the U.K. (Section 2.9.4). This may be apparent if the

patients continuing to be prescribed opioid medicines had different characteristics to those that had just started to take opioid medicines.

A previous study that has looked at the relationship between long-term opioid medicine use (greater than four prescriptions in a year) and prescribing of strong opioids and mental health diagnoses [27] used diagnostic codes only within the year of the study. Foy et al. [27] identified that patients with a mental health disorder were 1.12 (adjusted odds ratio) more like to have received 4 prescriptions in one year. However as this study only classified patients as having a mental health problem if a diagnostic code appeared in the current year, it is possibly not very sensitive to detecting patients with mental health disorders. A study [183] evaluated the positive predictive value (PPV) of a number of algorithms to correctly identify patients with the common mental disorders of anxiety and depression in Welsh primary care data matched with a community mental health survey (which used a positive diagnosis for anxiety and depression on the survey as the gold standard). As this was a community survey it is possible that patients did not present to their doctor with these symptoms. This study identified that this method was associated with a sensitivity of 0.06 (proportion of cases detected) and so was likely to underestimate whether a patient was anxious or depressed. In comparison, current treatment for anxiety and depression had a sensitivity of 0.48, a specificity of 0.89 (proportion non-cases detected) and a PPV of 0.68. (probability that person is identified is a true positive). Of the other 9 algorithms only one algorithm had a higher slightly higher sensitivity (0.49). Other algorithms had a higher PPV, but only because the specificity was not as high. This may have been in part due to antidepressants used for other condition such as chronic pain. In this study tricyclic antidepressants (TCAs) and duloxetine were excluded from the list of antidepressants (as these drugs are used for chronic pain) which could potentially increase the specificity further. Both methods will be used as a comparison in this chapter.

An additional analysis that is included in this chapter aimed to see whether it was possible to understand from CPRD what opioid medicines were likely to be prescribed for. This is because previous studies that measure long-term use of opioid medicines [1] have used

data from patients with specific indications (e.g. patients with musculoskeletal codes) who are prescribed opioid medicines but no study has identified what the majority of patients are receiving opioid medicines for. This is important in this study as it would be interesting to know whether it is possible to determine within CPRD what patients are taking opioid medicines for and to see whether patients with certain indications are more likely to take opioid medicines for longer periods of time.

3.2. Aims and objectives

Aims: Define a cohort of opioid medicine users that can be followed up long-term

Objectives:

- To extract a cohort from CPRD
- To compare the characteristics of the cohort with other data sources
- To compare characteristics of new and existing users of opioid medicines
- To determine how likely it is that the indication is recorded by prescribers when patients within the cohort start receiving prescriptions for opioid medicines

3.3. Methods

A flow chart of the cohort selection and analyses for Chapters 3 and 4 can be found in Appendix 1.

3.3.1. Study design, data source and time frame

This chapter reports the characteristics of patients from a proposed cohort study using U.K. primary care prescribing data extracted from CPRD. The study in this chapter utilised CPRD data from a cohort of adult patients that were issued with a prescription for an opioid medication in CPRD at any point in the calendar year 2009. Data were extracted using the January 2015 build and so the maximum length of time a patient could contribute data was 6 years after 2009. The data also included the period before 2009 and this data was used to calculate characteristics before opioid use started, as CPRD began in 1987. This was the earliest time at which the data began.

3.3.2. Study cohort

Opioid medicine users in 2009 were extracted from CPRD. Patients who had been recorded to have been prescribed an opioid prescription (identified via product code list see Appendix 2) at any point within the year 2009 were identified. The list of patients who were identified as having an opioid product code at any point in the year 2009 was then used to extract all data available for these patients. The data that was extracted contained all records that were available in the database for a particular patient.

3.3.2.1. Identification of patients with prescriptions for opioid medication

Patients were identified as receiving prescriptions for opioid medication if their records contained product codes for the opioid medications listed in Appendix 2. These codes are for opioids listed in chapters 4.7.1 and 4.7.2 of the BNF (BNF issues from 2000-2014).

However, certain product codes (and therefore prescriptions relating to these product codes) were excluded, these were for:

- Parenteral prescriptions and suppositories, as these preparations are not normally in the community setting for chronic pain.
- Diamorphine as this drug is not normally used in the community setting for chronic pain.
- Methadone, Buprenorphine 2mg 8mg sublingual tablets or buprenorphine 400mcg sublingual tablets prescribed by a brand that indicates the patient is being treated for opioid dependence (i.e. subutex), as these preparations are used to treat opioid dependence.
- Codeine strengths less than or equal to 15mg/5ml linctus, as this strength is used for the treatment of cough (NB codeine tablet strengths of 8mg 15mg and 30mg were included in the list of product codes).

3.3.2.2. Exclusions of patients from the extracted data

3.3.2.2.1. Patients under the age of 18 at their first prescription

Patients under the age of 18 when they were first prescribed any opioid were excluded from the data. This is because paediatric patients are likely to suffer from different diseases and are managed in a different way to adult patients [22].

3.3.2.2.2. Patients with a cancer diagnosis

Patients were identified as cancer patients if they had a cancer diagnosis at any point in their record. Cancer patients were identified as such if they had a Read Code from the Quality and Outcomes Framework Expanded Clusters list of Read Codes identifying “codes for relevant malignancies” v 30.0 [184]. This list of cancer codes was chosen based on an analysis of cancer Read Codes from various studies which measured cancer occurrences in CPRD [185-187]. The analysis identified that, in addition to the QOF codes which identified most cancer patients, using extra cancer Read Codes the studies which were additional to the QOF codes found patients with codes from the “morphology of neoplasms” group of cancer codes. The morphology of cancer codes identify that the patient has neoplasms

which may or may not progress to cancers that require pain control. However, these codes were not accompanied by where these cell changes occurred and so could not be used as a predictor of the likelihood a patient was prescribed an opioid for cancer (personal communication Barbara Heyes PRIMIS group University of Nottingham). Therefore the QOF codes were chosen as they were the codes that GPs were likely to use to identify cancers in patients they were currently managing in order to meet QOF requirements and therefore likely to have active cancer.

3.3.2.3. Patient registration requirement

Patients were required to have current registration dates before their first opioid prescription in 2009 and to be from a surgery that was deemed up to standard at their first opioid prescription in 2009 (Section 2.14).

In this chapter patients were excluded if they had less than one year of registry at an up to standard surgery before their first prescription in 2009. This was necessary to identify them as new or existing users of opioid medicines.

3.3.2.4. Missing or impossible prescription dates

Patients with missing or impossible prescription dates were excluded from the analysis. Patients who appeared to be prescribed all prescriptions after leaving the cohort were also excluded. This was because these dates may have been entered in error or may have been prescriptions that were entered into the patient's record much in advance of being dispensed.

3.3.3. Data management

3.3.3.1. Duplicate management

Prescriptions that were issued on the same day for the same product name and form, quantity, strength and dose were removed. This is because it is assumed that it is more likely

to be an administrative error than for a patient to require a prescription for an identical item on the same day.

3.3.4. Outcome measures

For schematic of outcome measures see Figure 3.

3.3.4.1. Prevalence of opioid usage in the U.K. during 2009

The total number of opioid medicine users extracted from CPRD using the method described in Section 3.3.2.1. was used as the numerator in the prevalence calculation. The total number of people in CPRD in 2009 was used as the denominator in the prevalence calculation. The total number of people in CPRD in 2009 was determined using the patient file provided with each CPRD build which provides a list of all patients that contribute data to CPRD within a particular version of the database. This list contains patients that contribute any amount of data from any time period in CPRD. The number of patients that contributed to the data within 2009 was calculated from the list of patients within the patient file by counting the number of patients that were registered at an up to standard surgery at any point in the year 2009.

3.3.4.2. Definition of new and existing users

Patients were defined as existing opioid medicine users if they were prescribed a prescription for an opioid medicine in the 180 days before their first prescription in 2009.

3.3.4.3. Definition of opioid medicine drug types

The opioid medicine drug type (e.g. morphine, codeine, etc…) on each prescription was extracted from the product name.

3.3.4.4. Age

Age was calculated as age the patient would be in the year 2009. Age was grouped into three categories 18-49, 50-64, 65+ years. This was to allow comparison to the study by Foy [27].

3.3.4.5. Gender

Gender was used as it was recorded in CPRD.

3.3.4.6. Socioeconomic status

Townsend scores measured in 2001 assigned to the patient postcode were used as a measure of deprivation. Townsend scores are calculated based upon 4 measures: proportion of the population employed, proportion of households that own a car, proportion of households not owning their own home, proportion of households with more than one resident per room [179]. These scores allow patients to be ranked in order of deprivation and the deprivation quintile in which an area is located is used as a marker of relative deprivation. Townsend scores are only available for patients from surgeries in CPRD that have consented to linkage and so a large proportion of the cohort do not have Townsend scores.

3.3.4.7. Categories of opioid medicine potency types

The opioid medicine potency types were divided into the following categories based on the combinations of drugs prescribed to patients: weak, weak and tramadol, tramadol, strong, strong and weak, strong and tramadol, all types of opioid medicine potency type. Tramadol is assigned weak and strong opioid status depending on the reference source and so it treated as a special case (Section 2.3.3). The potency types assigned to each opioid medicine drug type are provided in table (Table 3). The types of opioid prescribed in the first quarter (first 91 days) of a patient's record after their first prescription in 2009 were tabulated. Also all prescriptions in the patient record which occurred after 2009 were analysed to see what proportion of patients were prescribed a strong opioid before the end of their treatment. This was to assess what proportion of patients in each category were likely to change to different medications and to provide an impression of the likelihood of progression to other opioid medicines.

Table 3 Potency categories of opioid medicine drug types

Weak	Strong	Other
codeine	Morphine	tramadol
dihydrocodeine	Buprenorphine	
meptazinol	Fentanyl	
dextropropoxyphene	Oxycodone	
pentazocine	Pethidine	
	Dipipanone	
	Hydromorphone	
	tapentadol	

3.3.4.8. Physical comorbidities

Comorbidities were defined using the Quality and Outcomes Framework conditions (QOF). This was because the QOF aim is to identify the most common chronic diseases and they may be more reliably coded due to the fact that GPs are incentivised to use codes for particular diseases. Previous studies of multimorbidity have used QOF codes to define comorbid conditions [188]. Patients were identified as having a comorbidity if they had a Read Code from the list of expanded cluster Read Codes version 30 [184] which occurred at any point before the first opioid prescription in 2009. Depression was excluded as was rheumatoid arthritis and palliative care. This is because a separate depression and anxiety list of Read Codes was taken from another study and rheumatoid arthritis and palliative care were used in the pain indications section rather than including within the comorbidity criteria (Table 4). Physical comorbidities were measured to see whether it was likely or not that patients were being treated for other conditions and not just pain to give an impression of the types of patients using opioid medicines. A measure of comorbidity was included as previous studies had linked comorbidity to an increased probability of receiving strong opioid medication [27, 28].

Table 4 Physical comorbidities identified using Read Codes as per the Quality and Outcomes Framework v30

Quality and Outcomes Framework v30 Expanded Cluster Codes
Hypertension diagnosis codes
Asthma diagnosis codes
Ischaemic heart disease codes
Codes for diabetes
COPD codes
Chronic kidney disease codes 3-5
Osteoporosis diagnosis codes
Atrial fibrillation codes
Heart failure codes
Peripheral arterial disease
Stroke diagnosis codes
Epilepsy diagnosis codes
Stroke or TIA codes
Psychosis, schizophrenia + bipolar affective disease codes
Codes for Dementia
Learning Disability codes

3.3.4.9. Common psychological co-morbidities

The common psychological comorbidities of anxiety and depression were identified using two methods: the first based on the patient ever having Read Codes for diagnosis or symptoms of anxiety and/or depression in their medical records and the second based on antidepressants prescribed in the year before and the year after the first opioid prescription in 2009. The Read Code lists for anxiety were derived from studies by Windfuhr [189] and John [183]. However, patients were not included as having anxiety if they only had codes from these lists that appeared to be linked to chronic pain (e.g. headache) or appeared to be not specific anxiety codes (e.g. fear of flying) (see Appendix 3).

In addition to diagnostic codes being included in the anxiety and depression code list, symptomatic codes were also included. This was because a study by Rait [95], which looked at the incidence rates of depression (identified by diagnostic codes for depression) in comparison to community surveys, found patients coded with diagnostic depression codes

had fallen and coding of symptoms had increased. The Read Code lists for depression included the QOF depression codes “depression diagnosis Read Codes” [184] and a study by Kendrick which included depressive symptom codes in addition to diagnosis codes [190]. Depression codes can be found in Appendix 4.

Antidepressant product code lists from sections of the BNF 040301-040304 were collected as described in Appendix 5. Prescriptions for tricyclic antidepressants and duloxetine were excluded as these drugs are potentially used for the management of neuropathic pain (as recommended by NICE [131]) and so would not specifically identify patients with depression or anxiety. Patients were classed as receiving an antidepressant drug if they had a prescription for an antidepressant drug in the year either side of the first opioid prescription in 2009.

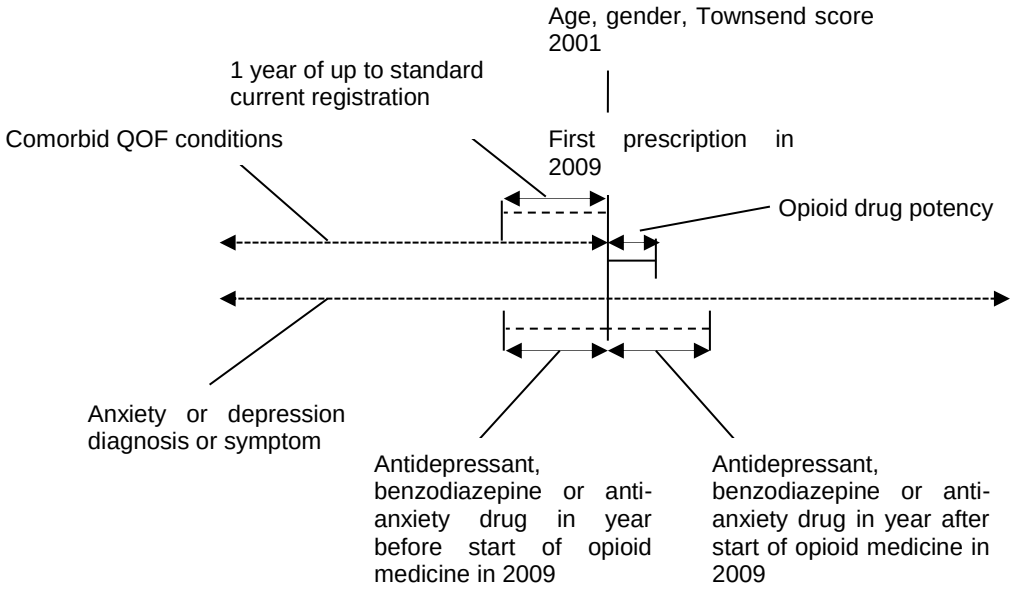
3.3.4.10. Benzodiazepine and anti-anxiety drug use

Lists of benzodiazepines and anti-anxiety drugs from BNF sections 040101 – subsection benzodiazepines and 040102 [191] were created using the same method as the opioid and antidepressant list see Appendix 6. Patients were classed as receiving a benzodiazepine or anti-anxiety drug if they had a prescription for a benzodiazepine or anti-anxiety drug in the year either side of the first opioid prescription in 2009. These drugs were included, as studies have identified that concurrent use of benzodiazepines was associated with risk of overdose and of identifying patients with drug misuse issues (Section 2.12) and may also identify if a patient is being treated for anxiety (identified by the use of anti-anxiety drugs).

3.3.4.11. Length of use of opioid medicines before 2009 (existing opioid medicine users only)

The length of time the existing patients had been continuously receiving prescriptions for opioid medicines before the first prescription in 2009 was calculated by tracing back through the prescriptions and measuring the time between prescriptions until there was a gap of greater than 90 days between the end of one prescription (as per Section 4.3.2) and the next. The date of the prescription after the gap was used as the date of the first prescription

Figure 3 Diagram of the method of measuring patient characteristics at first prescription in 2009



in what was termed an opioid "run". This was so it could be understood how the history of opioid use varied between the existing opioid users.

3.3.4.12. Registration status of existing opioid medicine users before 2009

The length of time that a patient had been registered at an up to standard surgery was also calculated at the time the patient was prescribed their first prescription in a run. This was because it is possible that patients joined the surgery whilst taking opioid medicines, which would mean they were potentially taking opioid medicines for longer periods at their previous surgery. By measuring the proportion of patients that were taking opioid medicines when they joined the surgery this would give an impression of whether patients were likely to have been receiving opioid medicines for longer than as calculated from the data.

3.3.4.13. Pain code lists

Lists of potential Read Codes identifying chronic painful conditions were included in the original Independent Scientific Advisory Committee (ISAC) protocol (2.14), this was compiled by Dr Suraya Zin and reviewed by Professor Roger Knaggs and Dr. Li-Chia Chen. This list was reviewed by Dr. Amelia Taylor and updated to include text word searches of the CPRD medcode library in order to produce a more comprehensive list of chronic pain conditions

(Table 5). In addition to these codes, Read Codes for musculoskeletal diseases were also requested from Jordan et al. Keele University [192] and added to the Read Code list. This pain code list from the group at Keele had been grouped into categories by area of the body. This list incorporated an area name “unspecified” which corresponded to musculoskeletal codes that did not relate to a specific part of the body, for example, “muscle pain”. For a list of the Read Codes used for pain code extraction please see Appendix 7 (The Keele codes are not included in this list as the list is long and the authors have requested that researchers contact them directly for this list). Extra pain codes were grouped into body area if possible so they could be grouped with the Keele Musculoskeletal Codes. If this was not possible they were grouped as diseases.

Table 5 List of key words used to search the Clinical Practice Research Datalink (CPRD) medcode list in order to develop pain code lists

Indication	Key word	Notes
Kidney stone	stone	Manually selected all kidney/ renal definitions
Pancreatitis	pancreatitis	Removed only code for history of*
Abdominal pain	abdominal pain	Removed no abdominal pain
Crohn's Disease	crohn	Removed if Crohn's colitis, categorised as colitis
Colitis	colitis	
Migraine/ headache	migraine/ headache	Removed 'no headache'
Pelvic pain	pelvic pain	
Osteoarthritis		
Rheumatoid arthritis	arthritis	
Arthritis unspecified		
Fibromyalgia	fibromyalgia	
Neuropathic	neuropathic	
Postoperative pain	postoperative	
Ankylosing spondylitis		Zin et al
Psoriatic arthropathy		Zin et al
Rheumatoid arthritis		Zin et al
Back pain		Zin et al
Diabetic neuropathy		Zin et al
Neck pain		Zin et al
Osteoarthritis		Zin et al
Phantom limb pain		Zin et al
Post herpetic neuralgia		Zin et al
Spinal pain		Zin et al
Trigeminal neuralgia		Zin et al
Palliative	palliative	
Cancer		QOF codes
Ulcer	ulcer	Manually selected all codes for leg ulcers or care of leg ulcers

3.3.5. Data analysis

The results in this chapter are reported as descriptive statistics. Patients receiving prescriptions for opioid medication were grouped into new users of opioid medication and existing opioid medicine user subgroups. Descriptive statistics were used to report outcomes variables for both the new and existing opioid medicine users.

3.3.5.1. Prevalence of opioid use

The prevalence was reported as the proportion of patients (percentage) contributing data to CPRD within 2009 who were prescribed an opioid medicine.

3.3.5.2. Comparison between dispensing data and CPRD data

The proportion of prescriptions (percentage) for each opioid medicine drug type as a total of all prescriptions was calculated. This was compared to the proportion of prescriptions for each opioid medicine drug type from the English NHS dispensing data described in (2.4.1).

3.3.5.3. Demographic characteristics

Age in 2009, gender and deprivation quintile were reported as percentages split into new and existing opioid user groups.

3.3.5.4. Drug characteristics

The drug potency types used at the start of the study (first quarter in 2009) were reported as percentages. In addition if a patient had ever received a strong opioid or tramadol at any point in their follow up, this was also reported split into new and existing opioid user groups.

3.3.5.5. Comorbidity characteristics

Number of QOF comorbidities, usage of antidepressants, diagnostic and symptomatic anxiety and depression status and use of benzodiazepines and/or anti-anxiety drugs were reported as proportions split into new and existing opioid user groups.

3.3.5.6. Length of time existing opioid medicine users had been receiving prescriptions for opioid medicine

The time between the first prescription in a run and the first prescription in 2009 was tabulated for all existing patients. The aim of this analysis was to see how long patients had been using opioids before 2009.

3.3.5.7. Length of up to standard registration in existing opioid medicine users

A separate analysis was performed for patients that had one year of up to standard data as a registered patient before their first run as a subgroup analysis.

3.3.5.8. Pain codes associated with start of usage

Pain codes were extracted from the new and existing opioid medicine user patient records if they were dated as the same date as the start of opioid use. For new opioid medicine users this was the first opioid prescription in 2009. For existing opioid users this date was earlier (Section 3.3.4.11). This was because the prescriber should add the code for the possible indication on the day of prescribing. This was to see whether patients were coded with a chronic pain related condition and to see what possible indications may occur around the time of first prescription. In a separate analysis Read Codes were extracted if they occurred at any point in the three months either side of the opioid medicine start date. This was to see if it was likely that the prescriber had added codes for a condition that the opioids may have been used to manage around the time of prescribing rather than just on the day.

CPRD users are instructed to add codes for a new diagnosis or when treatment has changed, therefore it is expected that patients should be coded with likely indications on the day of their first prescription and that new users and existing users should both be coded with likely indications. This analysis will show whether this is the case.

The proportion of patients that were coded with a pain Read Code (an area or disease) in the new and existing opioid medicine user groups was tabulated. The number of different pain areas per patient within each time period was recorded. This analysis will identify if patients were likely to have multiple pain areas. The proportion of patients with each pain code was reported (split into areas and diseases) and the percentages of patients with a particular code of the patients who were coded was calculated.

3.3.5.9. Software

All analyses were conducted using Stata v13 2013 (StataCorp College Station, TX)

3.3.5.10. ISAC approval

ISAC approval was granted for this project, protocol number 12_007 March 2012.

3.4. Results

3.4.1. Prevalence of opioid usage in the U.K. during 2009

The number of patients extracted from CPRD due to having a prescription for any opioid in 2009 was 622,516. In 2009, in CPRD, the number of patients in the database that were recorded as having data of sufficient quality for analysis was 5,212,511. Therefore the point prevalence of opioid use is calculated to be 11.94%. In 2009 the U.K. population was estimated to be 62.26 million people[193], this equates to approximately 7.4 million people receiving at least one prescription for an opioid medication in the UK in 2009.

After excluding children and patients and prescriptions not meeting up to standard data requirements, 604,476 patients with 14,129,319 prescriptions remain after 2009. Of these patients 68,658 (11.36%) had a cancer code within their record. When only including non-cancer patients with one year of up to standard data in their record before first prescription in 2009 495,512 remain. Of these non-cancer patients 290,296 patients (58.6%) were new users of opioid medication.

3.4.2. Comparison of the types of opioid medication in dispensing data and CPRD

The proportion of prescriptions for each drug type in the CPRD cohort was very similar to the dispensing data (Table 6).

Table 6 Proportion of prescriptions in the Clinical Practice Research Datalink (CPRD) and dispensing data for different opioid medicine types

Opioid drug type	% prescriptions CPRD	% prescriptions dispensing data
codeine	49.76	50.46
tramadol	17.73	17.85
dihydrocodeine	17.25	16.78
morphine	5.86	6.32
buprenorphine	3.06	2.89
fentanyl	2.63	2.62
oxycodone	2.52	2.21
dextropropoxyphene	0.66	1.00

3.4.3. Demographic and drug characteristics of the cohort

The majority of the new opioid medicine users were young (43.02% 18-49 years) whilst the majority of existing opioid medicine users were in the oldest age category (50.08% 65+ years). Most patients in both cohorts were female with slightly more in the existing group (63.82%) in comparison to the new opioid medicine user group (59.59%). There was a large proportion of Townsend deprivation scores missing (41.63%), due to the fact that not all surgeries had agreed to linkages with alternative data sources. However, for the patients that had a Townsend score, there is a higher proportion of patients in the lowest quintile in the existing opioid medicine user group (18.64%) compared to the new opioid medicine user group (15.45%) (Table 7).

Although the largest group of patients in the new opioid medicine user group were the weak opioid users (83.72%) and only 16.28% have strong opioids or tramadol in their first quarter of 2009, by the end of their time in the study 31.60% of patients have had strong opioids or tramadol. In comparison 30.03% of existing opioid medicine users were prescribed strong opioids or tramadol in the first quarter of 2009 which increased to 52.46% by the end of the study (Table 8).

Table 7 Demographic characteristics of the cohort of new and existing opioid medicine users in 2009

	Non-cancer New users[1] (n=290,296) (%)	**Non-cancer Existing users[1] (n=205,216) (%)**	**Non-cancer All users (n=495,512) (%)**
Age categories in 2009			
18-49	124,876 (43.02)	42,640 (20.78)	167,516 (33.81)
50-64	76,716 (26.43)	59,804 (29.14)	136,520 (27.55)
65+	88,704 (30.56)	102,772 (50.08)	191,476 (38.64)
Gender (% female)	59.59	63.82	61.34
Townsend score (Quintiles) 2001			
1 Least deprived	35,296 (20.42)	20,142 (17.31)	55,438 (19.17)
2	37,033 (21.42)	23,105 (19.86)	60,138 (20.79)
3	36,479 (21.1)	24,586 (21.13)	61,065 (21.11)
4	37,353 (21.61)	26,827 (23.06)	64,180 (22.19)
5 Most deprived	26,714 (15.45)	21,686 (18.64)	48,400 (16.73)
Missing (% cohort)	117,421(40.45)	88,870 (43.31)	206,291 (41.63)

Notes:

[1]New and existing opioid medicine users do not add up to the total number of patients as in order to ensure patients were new users or existing users they have to have a year's worth of up to standard data before first prescription in 2009 31,835 new users and 8,471 existing users did not meeting this criteria (see flow chart)

Table 8 Opioid medicine potency types prescribed to new and existing opioid medicine users

	Non-cancer New users (n=290,296)	Non-cancer Existing users (n=205,216)
Opioid medicine potency types in first quarter 2009		
Weak only	243,041 (83.72)	143,599 (69.97)
Tramadol only	25,850 (8.90)	28,006 (13.65)
Weak and Tramadol	13,327 (4.59)	13,889 (6.77)
Strong Only	4,109 (1.42)	9,795 (4.77)
Weak and strong	2,180 (0.75)	5,929 (2.89)
Tramadol and strong	894 (0.31)	2,660 (1.30)
Weak, Tramadol and strong	895 (0.31)	1,338 (0.65)
Any strong in first quarter	8,078 (2.79)	19,722 (9.61)
Opioid medicine potency type from 1st prescription 2009 to end of study		
Tramadol and/or strong	91,727 (31.60)	107654 (52.46)
Strong	24,489 (8.44)	46950 (22.88)

3.4.4. Comorbidity characteristics

The existing users of opioid medicines were more likely to have had one or more comorbidities with half of new opioid medicine users (50.32%) having no comorbidities in comparison to 30.69% of existing opioid medicine users. One in five existing opioid medicine users (20.15%) had 3 or more comorbidities in comparison to one in ten new opioid medicine users (10.37%). More patients in the existing opioid medicine user cohort were Read Coded as depressed and anxious at some point (51.07% of the new opioid medicine user cohort in comparison to 58.68% of the existing opioid medicine user cohort). Existing opioid medicine users were also more likely to have been prescribed an antidepressant in the year around the first prescription in 2009 (18.54% new users versus 25.97% of the existing users). Just over one in five (22.24%) of existing opioid medicine users had been prescribed a

benzodiazepine or anti-anxiety drug in the year either side of the first opioid prescription in 2009 whilst only 16.21% of the new opioid medicine users had received a prescription for a benzodiazepine or anti-anxiety in the past year (Table 9).

Table 9 Number of physical and psychological comorbidities of new and existing opioid medicine users

Characteristic	New users (290,296 pts) (%)	Existing users (205,216) (%)
Comorbidities before 1st opioid prescription 2009		
0	146,067 (50.32)	62,989 (30.69)
1	78,611 (27.08)	60,422 (29.44)
2	35,501 (12.23)	40,450 (19.71)
>3	30,117 (10.37)	41,355 (20.15)
Read Coded at any point in the data with depressed or anxious		
No	142,039 (48.93)	84,801 (41.32)
Yes	148,257 (51.07)	120,415 (58.68)
Antidepressant prescribed in year either side first opioid in 2009		
No	236,469 (81.46)	151,921 (74.03)
Yes	53,827 (18.54)	53,295 (25.97)
Benzodiazepine and/or anti-anxiety drug prescribed in year either side first opioid in 2009		
No	243,251 (83.79)	159,573 (77.76)
Yes	47,045 (16.21)	45,643 (22.24)

3.4.5. Length of time using opioids before 2009 in the existing patient group

Half of the existing opioid medicine users had been receiving opioids for less than 2 years. Approximately a quarter (25.61%) had been receiving prescriptions for greater than 5 years,

whilst 8.53% of the patients had between 10 and 20 years of continuously receiving prescriptions for opioid medicines (Table 10).

The vast majority of patients did have 1 year of up to standard registration before their first prescription in the run (78.43%). However, there is a clear decreasing trend with increasing time before 2009. For patients that started opioids between 10-20 years ago only just over a quarter of patients have a year of data before their first prescription, whereas for patients with less than a year over 90% have a year before (Table 10).

Table 10 Number of years of continuous use of opioids before first prescription in 2009 in existing users

Years before 2009	No. patients	%	Cumulative %	No. patients	%	Cumulative %	Proportion pts with 1 yr
	A1ll patients			Patients with 1 year before first prescription date			
>0-0.5	37,223	21.51	21.51	36,706	27.05	27.05	0.99
0.5-1	21,547	12.45	33.97	20,557	15.15	42.2	0.95
1-2	28,040	16.21	50.18	23,483	17.3	59.5	0.84
2-3	18,512	10.7	60.88	15,133	11.15	70.65	0.82
3-4	13,246	7.66	68.53	10,600	7.81	78.46	0.80
4-5	10,132	5.86	74.39	7,730	5.7	84.16	0.76
5-6	8,049	4.65	79.04	5,695	4.2	88.36	0.71
6-7	6,607	3.82	82.86	4,301	3.17	91.53	0.65
7-8	6,085	3.52	86.38	3,385	2.49	94.02	0.56
8-9	4,713	2.72	89.1	2,306	1.7	95.72	0.49
9-10	4,093	2.37	91.47	1,616	1.19	96.91	0.39
10-20	14,763	8.53	100	4,193	3.09	100	0.28
Total	173,010[1]	100		135,705	100		0.78

[1]32,206 existing users had a gap of 90 days between their first prescription in 2009 and the prescription before. This gives them a time before of zero days and so they are excluded from the analysis

3.4.6. Proportion of patients with pain Read Codes at the start of opioid medicine treatment

Only 46,610 (22.7%) patients who were existing opioid medicine users were Read Coded with a code from the pain lists on the day of their first opioid prescription. In comparison, 47.17% (136,927) patients were Read Coded with a code from the pain lists in the new opioid user cohort. Even when codes are collected from the time period three months either side of the first prescription, 48.30% of existing opioid medicine users do not have any pain codes whilst 32.13% of new opioid medicine users do not have any pain codes (Table 11).

On the day of the first opioid prescription patients were likely to have only one area code. However, one third (33.11%) of existing opioid medicine users had more than one area code within the 3 months either side of the first prescription and 29.28% of new opioid medicine users had more than one area code within the three months either side of the first prescription (Table 12).

In both existing and new opioid medicine user cohorts by far the largest group of codes present relate to back pain. In the existing opioid medicine user cohorts the three most common conditions were back, knee and unspecified, whilst in the new user cohort at both one month and three months, the most common codes are back, knee, and shoulder (Table 13, Table 14). The majority of the patients coded with a disease were coded with osteoarthritis in both the existing and new opioid medicine user cohorts (Table 15, Table 16).

Table 11 Proportion of patients with pain Read Codes at the start of opioid treatment

	No. patients with pain codes on day of 1st prescription (%)	No. patients with pain codes 3 months either side 1st prescription (%)	Total patients
Existing	46,610 (22.71)	106,090 (51.70)	205,216
New	136,927 (47.17)	197,010 (67.87)	290,296

Table 12 Proportion of patients with a pain code that have a single pain area Read Code

	No. patients on day of 1st prescription	No. patients 3 months either side 1st prescription
Existing	40,386 (96.21)	66,040 (66.89)
New	127,461 (96.85)	134,832 (70.72)

Table 13 Pain areas Read coded in existing opioid medicine users on the day of first prescription and 3 months either side of first prescription n=205,216

Pain area	No. patients with code on day 1st prescription (% of those coded)	No. patients 3 months either side 1st prescription (% of those coded)
No code for pain area	163,238	106,482
Back	13,326 (31.57)	28,999 (22.07)
Knee	4,938 (11.70)	12,789 (9.73)
Unspecified	2,941 (6.97)	13,531 (10.30)
Hip	2,802 (6.64)	7,064 (5.38)
Shoulder	2,595 (6.15)	7,716 (5.87)
Neck	2,531 (6.00)	6,990 (5.32)
lower back & lower limb	2,444 (5.79)	5,774 (4.39)
Head	2,114 (5.01)	7,234 (5.51)
lower limb	1,644 (3.89)	6,483 (4.93)
Abdomen	1,263 (2.99)	7,207 (5.48)
Chest	1,242 (2.94)	7,744 (5.89)
Foot	1,052 (2.49)	4,704 (3.58)
Pelvis	683 (1.62)	2,720 (2.07)
Ankle	603 (1.43)	2,801 (2.13)
Hand	494 (1.17)	2,358 (1.79)
upper limb	439 (1.04)	1,676 (1.28)
Elbow	365 (0.86)	1,681 (1.28)
Other	736 (1.74)	3,932 (2.98)

Table 14 Pain areas Read coded in new opioid medicine users on the day of first prescription and 3 months either side of first prescription n=290,296

Pain area	No. patients with code on day 1st prescription (% of those coded)	No. patients 3 months either side 1st prescription (% of those coded)
No code for pain area	158,989	99,629
Back	42,985 (33.48)	59,625 (25.03)
Knee	11,152 (8.68)	20,062 (8.42)
Head	10,060 (7.83)	17,242 (7.24)
Shoulder	9,513 (7.41)	16,333 (6.86)
Neck	9,149 (7.12)	14,517 (6.09)
lower back & lower limb	7,432 (5.79)	11,690 (4.91)
Chest	5,904 (4.60)	13,609 (5.71)
Hip	5,365 (4.18)	9,908 (4.16)
Abdomen	5,322 (4.14)	14,957 (6.28)
Unspecified	4,416 (3.44)	15,387 (6.46)
lower limb	3,538 (2.76)	8,894 (3.73)
Foot	3,381 (2.63)	8,779 (3.69)
Pelvis	2,996 (2.33)	6,432 (2.70)
Ankle	1,600 (1.25)	4,452 (1.87)
upper limb	1,490 (1.16)	3,328 (1.40)
Hand	1,208 (0.94)	3,885 (1.63)
Elbow	1,137 (0.89)	3,146 (1.32)
Other	1,760 (1.38)	5,978 (2.52)

Table 15 Diseases Read coded in existing opioid medicine users on the day of first prescription and 3 months either side of first prescription n=205,216

Disease	No. patients with code on day 1st prescription (% of those coded)	No. patients 3 months either side 1st prescription (% of those coded)
No code for disease	198,337	182,955
Osteoarthritis	3,818 (55.10)	11,135 (46.42)
Pain in joint – arthralgia	1,102 (15.90)	3,275 (13.65)
Arthritis unspecified	730 (10.54)	2,741 (11.43)
Rheumatoid arthritis	296 (4.27)	1,686 (7.03)
Fibromyalgia	199 (2.87)	722 (3.01)
Ulcer	199 (2.87)	1,441 (6.01)
Postoperative pain	108 (1.56)	251 (1.05)
Neuropathic	69 (1.00)	422 (1.76)
Crohn's disease	67 (0.97)	338 (1.41)
Ankylosing spondylitis	60 (0.87)	197 (0.82)
Colitis	58 (0.84)	386 (1.61)
Trigeminal neuralgia	56 (0.81)	244 (1.02)
Pancreatitis	50 (0.72)	336 (1.400)
Psoriatic arthropathy	46 (0.66)	198 (0.83)
Post herpetic neuralgia	34 (0.49)	193 (0.80)
Diabetic neuropathy	16 (0.23)	119 (0.50)
Palliative	10 (0.14)	196 (0.82)
Phantom limb pain	9 (0.13)	35 (0.15)
Kidney stone	2 (0.03)	72 (0.30)

Table 16 Diseases Read coded in new opioid medicine users on the day of first prescription and 3 months either side of first prescription n=290,296

Disease	No. patients with code on day 1st prescription (% of those coded)	No. patients 3 months either side 1st prescription (% of those coded)
No code for disease	282,731	269,530
Osteoarthritis	3,664 (48.25)	9,407 (42.64)
Pain in joint – arthralgia	1,695 (22.32)	3,908 (17.72)
Arthritis unspecified	590 (7.77)	1,777 (8.06)
Postoperative pain	382 (5.03)	571 (2.59)
Ulcer	267 (3.52)	1,385 (6.28)
Rheumatoid arthritis	172 (2.26)	1,069 (4.85)
Fibromyalgia	153 (2.01)	433 (1.96)
Trigeminal neuralgia	152 (2)	424 (1.92)
Post herpetic neuralgia	124 (1.63)	446 (2.02)
Palliative	74 (0.97)	622 (2.82)
Neuropathic	69 (0.91)	434 (1.97)
Colitis	52 (0.68)	444 (2.01)
Pancreatitis	51 (0.67)	323 (1.46)
Crohn's disease	43 (0.57)	243 (1.1)
Kidney stone	33 (0.43)	255 (1.16)
Psoriatic arthropathy	30 (0.4)	167 (0.76)
Ankylosing spondylitis	24 (0.32)	77 (0.35)
Diabetic neuropathy	11 (0.14)	62 (0.28)
Phantom limb pain	8 (0.11)	12 (0.05)

3.5. Discussion

3.5.1. Prevalence of opioid medicine use

This study found that 11.94% of the population received opioid medicines in 2009. Two large studies have reported the proportion of patients that received opioid medication within a year. Foy et al. [27] (Leeds/Bradford England, n=85,022 receiving opioid medicines, prescribing data from electronic health record) reported that in 2009-2010 11.22% of patients received opioids for non-cancer conditions. The prevalence reported in this chapter included cancer patients, which may be the reason for the slightly higher estimate. In the study in this chapter 11.36% patients had a cancer diagnosis, therefore the percentage excluding cancer patients would be 10.58%. Ruscitto et al. [28] (Tayside Scotland, n=34,218 receiving opioid medicines 2010, dispensing data from community pharmacy) reported in 2010 that 11.0% of patients received opioids for both cancer and non-cancer conditions. As Ruscitto et al. study included cancer patients, it likely that opioid prescribing in Scotland is slightly less than England. These results appear to be similar and so it can be concluded that CPRD has the same proportion of opioid medicine users as other studies in the U.K.

In the non-cancer cohort of patients within the Foy et al. [27] study, 10.2% of patients received a strong opioid in 2009 (not including tramadol). In the study within this chapter, 5.6% patients received a strong opioid in the first quarter of use in 2009 and 14.42% of patients received a strong opioid during the whole time in the study. The number of strong opioid users in the data in 2009 will be in between these two limits making it consistent with the Foy study. This provides further evidence that the opioid prescribing data within CPRD is consistent with other data sources.

3.5.2. Comparison of the types of opioid medication in dispensing data and CPRD

The proportion of prescriptions written for each opioid drug type appeared very similar in the English dispensing data and the CPRD data (Table 6). This means that it is likely that the types of drugs that are prescribed by prescribers contributing data to CPRD are the same

types that are prescribed to the population. It is therefore likely that the results from this data can be extrapolated to the English population.

However, from the results of the Ruscitto [28] study it appears that prescribing in Scotland does vary in terms of the opioid drug types prescribed compared to the U.K. in that in Scotland fewer patients were prescribed buprenorphine. For example, in Scotland in 2009, 46,057 prescriptions were dispensed in 4.7.2 BNF group for buprenorphine, 228,272 for morphine [194]. Thus the ratio of morphine to buprenorphine prescriptions is 1:5. In the U.K. the ratio of buprenorphine to morphine to buprenorphine is approximately 1:1.9. CPRD includes data from Scottish practices so it is possible that this would affect the proportions of patients prescribed different opioid drugs as patients may be given other drugs rather than buprenorphine. However, only 11.3% of CPRD practices are located in Scotland [178] and so this may be a reason why the dispensing data for England is similar to prescribing data for CPRD. The data for Wales in 2009 was not available to compare. Thus CPRD data is likely to be representative, in terms of the opioid drug types prescribed in the U.K. overall but the results may be more generalizable to England rather than Scotland as this is where most of the practices are and there are differences in prescribing between the two countries.

3.5.3. Types of patients receiving prescriptions for opioids

This study found that a cohort of new and existing users of opioid medicines, overall were more likely to be older and female (of all the non-cancer patients the age group with the highest proportion of prescriptions was the over 65s (38.64%) and 61.34% of these patients were female) (Table 7). The prevalence of chronic pain is greater in older age groups [41] and women [84] are more likely to suffer with pain, therefore the increased requirement for pain relief may be the reason why these types of patients receive a greater proportion of opioid medicines. The main differences between the new and existing opioid user groups may be down to the fact the new users are mainly patients being treated for acute pain and the existing users those that are being treated for chronic pain.

The study by Foy et al. [27] is the only study to report the age and gender of patients receiving all types of opioid medicines in a large population with multiple pain conditions. When all patients in the Foy study are compared the largest group appears to be the youngest group with 41.08% of patients compared to the 33.81% in this study. The Foy study also reported the proportion of patients with four or more prescriptions, in this group a much higher proportion of patients is in the older age group (45.04%) which is closer to the 50.08% found in the existing users of opioid medicine within the study in this chapter. The reason for the discrepancy in the overall data may be because the current study uses data from CPRD, which contains patients which reflect the age and gender characteristics of the current U.K. population [178], whilst Leeds, as with other cities, has a disproportionately high number of younger people [195]. The younger people may be more likely to receive prescriptions for acute pain in the short term than in the general population and so there could be a higher proportion of acute opioid medication users in the Leeds/Bradford area. In both the Foy study and the study within this chapter a higher proportion of all patients are female (61.34% current study vs 60.87% Foy study). Higher proportions of the existing users are female in the current study (63.82%) similar to the proportion of patients that receive greater than four prescriptions in the Foy study (63.1%). Thus, a similar proportion of patients within the 2009 cohort are women and the possible reasons for the difference in age can be explained by the cohort selection.

Patients were more likely to have physical comorbidities before first opioid prescription in 2009 in the existing opioid medication user group compared to the new opioid medicine user group. Just over two thirds of patients in the existing opioid medicine user group had at least one other long-term condition (and this did not include depression) with one in five having at least 3 physical comorbidities. Twice as many patients in the existing opioid medication user group had greater than 3 physical comorbidities than in the new user group. The existing opioid medicine user group are likely to be different from the new user group as the new user group will include patients using opioids for acute use. The existing opioid medicine user group is more likely to consist of patients with chronic pain and so have characteristics of

patients with chronic pain. As 80% of patients with greater than three long-term conditions have chronic pain [42] patients with chronic pain are likely to have more comorbidities than the general population.

The study in this chapter found a higher proportion of patients had been prescribed an antidepressant (TCAs and duloxetine excluded) in the year around first prescription in 2009 in the existing opioid user group (25.97%) than the new opioid medicine user group (18.54%). Over half of both new and existing opioid medicine users groups had ever been Read coded with a diagnostic or symptom code for anxiety and depression (51.07% and 58.68% respectively). In the general population, the proportion of patients that report ever being diagnosed with a common mental disorder (CMD) confirmed by a professional is 20.0% men and 34.5% of women [81]. Thus the occurrence of anxiety and depression appears to be almost twice as high in the cohort of opioid medicine users than in the general population. A high proportion of patients have anxiety or depression and so this may indicate why there is a higher proportion of patients with anxiety or depression in the existing patient group. However, there is still the possibility that “adverse selection” could possibly happening in U.K., in that patients who have been receiving prescriptions for longer are more likely to have symptoms of depression and/or anxiety.

Two methods of measuring whether the patient was likely to have common mental disorders (CMD) were used in this study: (1) a sensitive method which included classifying patients as ever having received a diagnosis or symptom of anxiety and depression and also (2) whether a patient was prescribed an antidepressant at the time of first opioid prescription in 2009. Many more patients were identified as anxious or depressed (having a CMD) at some point using the ever diagnosis or symptom method compared to those recorded as having been prescribed an antidepressant at the time of first opioid prescription in 2009 (one year either side of first prescription 2009). However, patients were recorded as being anxious or depressed if they ever received a Read Code for depression or anxiety diagnoses, or symptoms whilst the antidepressant prescribing had to be within a certain time period (one year either side of the first prescription in 2009).

Previous U.K. based cross sectional studies have found that long term opioid patients were more likely to have a mental health diagnosis. In future chapters of this study both measures will be used to provide a point of comparison.

A large proportion of patients did not have a deprivation (Townsend 2001) score because this variable is only available for practices that agree to linkage of data. Data linkage is only possible in English practices [178] and so any further analysis that includes deprivation will only represent data from England. In the analysis of the demographics of patients taking opioid medicines, the proportion of patients receiving opioid medicines who are in the lowest quintile group is lower than the proportions in the other groups. This could imply that patients are less likely to be prescribed opioids if they in the most deprived groups. This is contrary to the findings of other studies that have identified that prescribing of strong opioids is more likely in more deprived areas [28]. Studies have found that deprivation is associated with an increased probability of long-term use [27] in the U.K..

Patients who are in the lowest income quintile are also more likely to report that they have chronic pain [44]. However, it is possible that CPRD data is not representative in terms of deprivation and the low numbers of patients in this group represent low numbers of patients from more deprived areas. A difference is seen between the new and existing users in that there is a higher proportion of patients in the most deprived quintile in the existing users than in the new users of opioid medicines (15.45% new users most deprived quintile vs 18.64%). This is again likely to there being more chronic pain patients in the existing user group and is consistent with other studies.

3.5.4. Proportion of patients coded with possible pain indications

In CPRD all consultations in which a change of therapy occurred should be Read coded with morbidity codes [196]. Only 22.7% of patients in the existing opioid medicine user group and 47.17% in the new opioid medicine group were Read coded with a code from the pain lists on the day of their first opioid prescription in the run. This could either be because the code lists do not include all the Read Codes for conditions, or that prescribers contributing data

are not entering codes on the date that new opioid therapy starts. As the pain code list contained a comprehensive list of all musculoskeletal codes it would mean that these patients have non-musculoskeletal conditions that have not been included or that prescribers are not adding codes for these conditions. Analysis in subsequent chapters will involve looking at the proportions of patients taking opioids in the long-term. The probabilities calculated as a result of this work would be more useful if they were only calculated in patients with chronic pain conditions. By using a Read Code for chronic pain, with a standard definition, this would allow more comprehensive research to be conducted on this group of patients.

A larger proportion of patients are Read coded with potentially painful conditions if a larger time frame of three months is used. However, as many patients with chronic pain have multiple pain symptoms [197] it is possible that these codes may not be the original indication for what the opioid is prescribed for. The analysis within this chapter showed that counting numbers of areas of pain in the body within 3 months either side of the first prescription in 2009 identified that a large proportion of patients had multiple pain codes. However, the lists of pain codes included non-specific codes such as “general aches and pains” therefore this could have just been due to duplicate coding. Also, there were two codes that referred to back pain; back pain and lower back pain, this could have increased the number of patients who were coded with multiple pain areas when the pain may have been in one area. However, evidence for this is suggested by more recordings of codes such as abdominal pain which could potentially be a side effect of the new opioid or previous medication though this will not be true in all cases as a number of patients are coded with abdominal pain on the day of their first prescription.

A better method of linking indication to opioid use is required in order to improve the specificity of cohort selection. A further study to examine whether this is the case would involve linking codes to certain prescribing features such as a change in opioid prescription or strength, a referral, or an increase in dose. Studies may need to use different methods e.g. machine learning techniques or review individual records at GP surgeries to identify

whether this is the case. This would then need to be validated by asking prescribers if this was the original indication for the opioid medicine. It is important that research is conducted to link indication before further work is conducted using the indications within CPRD, or that a better understanding is obtained of how and why prescribers code patients with a certain indication in a large study of prescribers. This is because prescribers may be more likely to code certain patients with indications and this will introduce bias into the sample.

In this study back, knee, general (unspecified) hip and shoulder pain were found to be specifically associated with pain on the day of first prescription in the existing user group whilst in the new user group back, knee, head, shoulder and neck were the most common conditions on the day of first prescription.

Back pain is repeatedly shown to be the most common reason for consulting. A survey of GP records at 12 general practices during 2006 [192] (this survey was the original study from Keele from which the musculoskeletal codes were obtained) found that the most common musculoskeletal conditions were back pain, lower back pain, knee pain, chest pain and neck pain. However, this was a survey of patients presenting with incident and prevalent pain conditions so may not reflect the conditions suffered by chronic pain patients who were likely to be prescribed opioids [192]. In comparison a telephone survey including chronic pain patients (n=4,839) (patients experiencing pain for at least six months) in 15 European countries found that the most common persistent conditions were back, lower back, knee, head and leg pain. [45] Thus, headache is also a common cause of chronic pain. In the 2012 National Pain Audit [128], low back pain was the most common condition, with lumbago with sciatica the next most common. Next was cervicalgia (neck) and then pain in joint. This is likely to reflect patients with problematic persistent pain as the patients have actually got to the stage of being referred to the pain clinic. However, the audit report remarked that the groups of patients seen exclude certain groups that, based on the prevalence of certain types of pain (e.g. visceral pelvic), means that this survey is not completely representative of persistent pain types. [128] Therefore, the main codes used are representative of the most

common pain conditions. However, as mentioned before, this could just be representative of concomitant pain conditions rather than the primary reason for opioid use.

Due to the fact so many patients have indications missing on the day of first prescription, future analysis will not include only patients with certain indications as this will potentially lead to a biased sample.

3.5.5. Strengths and limitations

This is a study of opioid prescribing in a large representative U.K. population and included all opioids prescribed to patients that are likely to have been prescribed to treat pain. This study also divided patients into new and existing groups to at least partially take into account the length of prescribing before the first prescription in 2009.

A limitation of this study is that the data source only relates to prescribed opioids and so over the counter opioid use will not be captured. This means that the length of opioid use could be underestimated if patients obtain supplies over the counter or if their GP stops prescribing opioids for them. As with all studies using prescribing data in general, it is impossible to know whether the patient is consuming the medication or not.

A further limitation is the fact the antidepressant, benzodiazepine and anti-anxiety drug use was measured in the year either side of the first prescription in 2009. It is possible that patients were never taking the medications at the same time and that the prescriber was trying out medicines in an attempt to find an effective treatment.

The length of time before first prescription in 2009 may have been underestimated because not all patients had one year of data before their first prescription in 2009 and some prescriptions may have been from before the surgery was deemed up to research standard. However, the analysis of length of time before receiving the first opioid prescription was not to calculate the proportion of patients who have been receiving opioids for a specific period of time, but just to see if this was possible and the proportion of patients in each group that did not meet this standard was reported. The fact that patients were not up to standard, or

currently registered when they first started receiving opioid medicines, means that the results from the existing user group is the minimum number of patients that have, for example, 3 comorbidities. To more accurately measure how these factors affect long-term use the cohort of new opioid medicine users who have a minimum of one year of data before their first prescription can be followed over time.

The fact that this study only measures the characteristics of patients receiving opioid medicines at one point in time does not show what groups are likely to be continuing opioid medicines in the long-term, for example what proportion of younger people continue to use opioid medicines, as they may be smaller in number but have the possibility of taking opioid medicines for many years. This does not show the different dosages on the prescriptions that the patients receive either and whether this is more likely in certain groups. As the patients within the existing users group only had to have one previous prescription before their first 2009 prescription there is a range of patients within this group so although there are differences between the groups which may identify that certain types of patients continue use (as these patients will accumulate over time). To understand how characteristics affect the probability of continuation of opioid medicine use an analysis of how these characteristics are related to the rate of discontinuation is required.

3.5.6. Summary

This study identified a cohort of patients from CPRD that were receiving opioid medicines. From the size of the cohort it was calculated that 11.94% of the U.K. population received an opioid in the year 2009. This is a similar prevalence estimate to studies that measured opioid prescribing in a comparable population. The age and gender structure of the cohort also appeared similar to another U.K. study that measured opioid use. The relative proportions of the opioid drug types to one another matched the relative proportions of opioids dispensed in England. The cohort can therefore be used in subsequent chapters for further analysis.

In this cohort 58.59% were new users of opioid medicines (had not received an opioid in the past 6 months) and 41.41% existing users of opioid medicines. A substantial number of

patients had been using opioids continuously prior to 2009; 25% of the existing users receiving continuous opioid prescriptions for at least 5 years. There was a difference between the proportion of patients with greater than 3 comorbidities with a lower proportion of patients in the new cohort (10.37%) having > 3 comorbidities compared to 20.15% in the existing users of opioid medicines. A higher proportion of existing opioid users were likely to receive antidepressants in the year before or after use. Though this is probably due to patients in the existing users having characteristics of patients with chronic pain, there is the possibility that adverse selection could be occurring (though by no means certain) within the U.K. Further work is required to explore how the characteristics of patients taking opioids change in relation to time. This will be done in the next chapter.

In this study only half of patients in the cohort had a pain type Read Code on the day of their first prescription in the new opioid medicine user cohort in comparison to 22.71% of patients in the existing opioid medicine user cohort. Therefore, a large proportion of patients that do not have an indication from the list of chronic pain conditions in their record for the opioid medicine they are prescribed.

Chapter 4. Measuring length of continuous use of opioid medicines and patient characteristics associated with long-term use

4.1. Introduction

In Chapter 3, it was found that 10.58% of the U.K. population received an opioid for non-cancer pain in 2009. The patients in the existing opioid medicine user group were more likely to be older women, have multiple comorbidities and were more likely to have been prescribed antidepressants or benzodiazepines and/or anti-anxiety drugs than the patients in the new opioid medicine user group. Therefore, there are some characteristics that are different in the new and existing users. However, the existing group is comprised of patients using opioids medicines for different periods of time so it is not currently known what characteristics are linked to long-term use.

In order to separate patients into a long-term group, it is necessary to define "long-term" use. In previous studies that look at persistence with opioid medicines, which have mainly looked at data from prescription records in large databases, a variety of methods have been used to define long-term use. These studies had the aim of highlighting that long-term use is increasing and associated with characteristics such as depression rather than being linked to any specific outcomes such as adverse events. Therefore, the purpose of the long-term measure in these studies is to show that over time a greater number of patients receive medication lasting over a particular "long-term" threshold. One such method, commonly used, involves defining a threshold value after which a patient is classified as a long-term patient. For example, in some studies from the U.S.A. [89, 125] and the U.K. [1, 27], "long-term use" has been defined in slightly different ways but most commonly >90 days treatment [125] (U.S) or ≥3 prescriptions [1] or ≥4 prescriptions (U.K.) [27]. This threshold method appears to be first used by Von Korff [125] and was based on the probability of patients continuing to be prescribed opioids in the future at different time points since starting and also to reflect the definition of chronic pain at the time.

However, in the U.K., it is not known whether patients with three or four prescriptions (as used in the U.K. studies) are likely to continue or discontinue use after this point and whether this definition is applicable to U.K. data. Also, by using this definition, it is not possible to see

whether and how the probability of continuation changes after this point. Additionally, this method assumes that patients who use opioid medicines frequently but intermittently at the start of their treatment will not become long-term opioid users. The only study that looks at the physical and psychological comorbidities of long-term opioid patients in a large U.K. population, in patients with all indications, uses this method (long-term use defined as greater than four prescriptions) [27]. This means that, in this study, the group of patients classified as long-term patients (and their associated characteristics) may contain patients who receive opioid medications for many years or just a few months and so that factors associated with long-term use may not be identified when patients are just divided into two groups and that patterns of opioid use that develop after this point will not be seen.

Other studies in the U.S.A. [96, 198] have determined length of use based upon the time to a gap (or time to interruption) in prescriptions from the start of opioid treatment, which has the benefit of measuring opioid usage over continuous periods of time. This method allows the probability to be calculated that a patient is continuing to receive prescriptions at each point in time and so allows rates of continuation/discontinuation to be compared between patient groups. This method allows the measurement of continuous use over a long period of time. In this study, continuous use of opioids is measured to attempt to select patients who are possibly being “adversely selected” for long-term treatment (Section 2.9.4) if this is happening in the U.K..

In this study, the time to interruption is used to determine the probability of continuing to prescribed opioid prescriptions without a break for all patients who received an opioid in 2009. The time to interruption requires a gap size between prescriptions to be defined (the definition of interruption) and this has differed between past opioid studies with different gap lengths being used [1, 199]. In other studies, which look at persistence with other types of medication, the recommended size of the gap is dependent on the pharmacological properties of the drug; i.e. the length of time it takes for blood levels to become sub therapeutic [200]. However, in this study, patients may have small gaps in treatment which are appropriate, as they use the medication as required rather than continuously, to treat

intermittent pain. Since the length of gap changes the proportion of patients who continue opioid medicine use, this study investigated a number of different gap sizes to understand the effects of changing the gap size.

The probability of continuation is plotted for new patients and also, to see whether the three prescription threshold is applicable in the U.K., the probability of a patient continuing to receive opioid prescriptions is calculated in patients who receive three prescriptions as a subgroup analysis. The probability of continuation in existing users of opioid medication, grouped by length of previous use, is also plotted to see how the length of time patients have previously been using opioid medication affects the probability of continuing to receive opioid prescriptions in the future and to see if similar patterns are found in existing users to new users. Previous opioid studies have identified that the length of time a patient has been receiving opioid medicines is related to the probability they will continue [97].

Once an appropriate measure of the length of opioid use has been developed, the second part of this chapter will examine the demographic and clinical characteristics associated with the rate of continuation of opioids in long-term opioid medicine users, specifically whether common psychological comorbidities are associated with the continuation. This is with the hypothesis that adverse selection may be occurring in groups of long-term opioid medicine users.

4.2. Aims and objectives

To identify what patient characteristics affect time to interruption/ probability of continuation of receipt of opioid medicine prescriptions in a group of opioid medicine users

- To examine the patterns of interruption/continuation of opioid use in new and existing populations and to define long-term use based on the probability of continuing to receive opioids at subsequent time points
- To describe how characteristics of patients affect the rate of continuation of long-term patients

4.3. Method

4.3.1. Study design, data source and time frame

This study is a retrospective longitudinal cohort study using the 290,296 new opioid medicine users and 205,216 existing opioid medicine users (Chapter 3). Patients were followed from their first prescription in 2009 until they had a defined gap (4.3.2.2) in their opioid prescriptions (e.g. at least x days (defined by sensitivity analysis) between the end of one prescription and the start of the next or no further prescriptions), death, or the end of the study (end of transfer of data into the CPRD database Jan 2015).

4.3.2. Outcome measures

4.3.2.1. Length of prescription

The length of the prescription was calculated by dividing the total quantity of medication on the prescription by the amount of medication used per day. This was done by using the numerical daily dose (ndd), if present. If no ndd was present the median length of prescriptions having an ndd for the same opioid drug and route of delivery (e.g. buprenorphine patches or co-codamol tablets) and quantity were used. If no other prescriptions for the same quantity and opioid drug and route of delivery had an ndd, the median length of prescriptions from the same opioid drug and route of delivery was used. The maximum length of the prescription was capped at 90 days. If prescriptions were calculated to be longer than this period or 0 days, the length of prescription was estimated to be 30 days.

4.3.2.2. Gap between prescriptions

The end date of a prescription was calculated by adding the number of days on the prescription to the prescription date. The number of days between the end of the prescription and the next prescription was calculated by counting the number of days between the end of the last prescription and the start of the next. This number is defined as the “gap” between prescriptions.

4.3.2.3. Reason for end of follow up

The end of follow up was defined as either last collection of data from the surgery, death date as defined within CPRD or transfer out date, whichever came first.

4.3.2.4. Length of continuous opioid medicine use

If the end of the last prescription before a gap occurred within the gap size of the end of follow up date, then the length of use was the number of days between the first prescription 2009 and the end of follow up date. The outcome was then the reason for the end of follow up. Otherwise, the length of use was the number of days between the first prescription 2009 and the end of the last prescription before a gap and the patient discontinued use.

4.3.2.5. Baseline characteristics potentially associated with long-term use

The same characteristics that were reported in the previous chapter: age 2009, gender, socioeconomic status, physical comorbidities before first prescription in 2009, anxiety or depression diagnosis or symptoms ever, antidepressant prescribing in the year before or after first prescription of opioid medicines in 2009, benzodiazepine and anti-anxiety drug prescribing in the year before or after first prescription of opioid medicines in 2009, were used in this chapter (Figure 3).

4.3.3. Data analysis

To define long-term use, the probability of continuation was measured by calculating the probability that a patient will still be receiving prescriptions for opioids (i.e. not had a gap in treatment) at different time points after the first prescription. However, as patients may leave the data due to death, leaving the surgery or when the surgery last contributed data, it is necessary to account for this. Kaplan-Meier curves are commonly used in cohort studies to deal with this problem. This method involves calculating the probability of a particular event occurring at different points in time after the start of the study. This is done at each time point by calculating the proportion of patients, that are still contributing data, that have an event at a particular point in time. In this case, the event is a gap in prescriptions at the time point.

The proportion of patients who continue opioid use at a particular time point can be calculated from the number of patients that do not have a gap.

However, there is also another complication when using time to event analysis when measuring the probability that a patient continues to take a medication: an outcome of the study is the proportion of patients who continue opioid medication as well as the proportion who interrupt their opioid medication. Patients who die whilst taking opioids do not fall into either of these categories and so death needs to be treated as an additional competing event.

To calculate the probability of both discontinuation and death, we can use competing risks methods. Competing risks give the cumulative incidence of several events over time, along with an estimate of the confidence intervals. Cumulative incidence is the probability of the event (either death or interruption) occurring before a particular time point. The analysis was carried out using the Stata extension outlined by Coviello [201].

4.3.3.1. Probability of all new and existing opioid medicine users continuing to receive prescriptions for opioid medicines; continuation defined by varying gap sizes

A sensitivity analysis was performed to see how the gap size used changed the proportion of patients continuing to receive opioid prescriptions (continuation defined as having no gap). Death was treated as an interruption of the medication in this analysis, as only the probability of continuation of opioid medication was plotted. The reason for doing this analysis was to judge the extent to which varying this gap affected the probability of continuing. Gaps of 30, 60, 90, 120, 150, 180 and 365 days between prescriptions were used in the variable gap size analysis.

The probability of patients continuing with opioid medicines at the end of 1, 2, 3, 4 and 5 years was plotted using gap size as the independent variable. This was plotted to see how the proportion of patients continuing to each time point changed as the gap size changes.

4.3.3.2. Probability of new users continuing to receive prescriptions for opioid medicines

This analysis measured the probability of continuation of opioid medication treatment from first prescription in 2009 until end of follow up, using a maximum permitted gap size of 90 days between the end of a prescription and the start of the next for new users of opioid medication. This was found to be an appropriate gap size in the previous analysis. In this analysis, death was treated as a competing risk.

4.3.3.2.1. Subgroup analysis: probability of new opioid medicine users with at least 3 prescriptions in their first quarter (91 days) continuing to receive prescriptions for opioid medication

Other studies that describe time to gap in prescriptions have excluded patients who have less than a certain length of treatment e.g. fewer than 3 prescriptions in 90 days, fewer than 90 days, as a way of limiting estimation of long-term use to only patients with chronic pain. This analysis looked at the probability of continuation to receive prescriptions for opioid medicines only in patients who had at least three prescriptions in their first 91 days (91 days was used as subsequent analysis involved dividing patients' treatments in quarters of the year which was defined as 91 days, (Chapter 5)).

To see how only including these patients affected the proportion that continue opioid medication, this study measured the probability of continuing to receive prescriptions for opioid medicines from first prescription in 2009 until end of follow up and included only patients who had at least 3 prescriptions for opioid medication within the first quarter. This analysis used a gap size of 90 days between the end of a prescription and the start of the next for new users of opioid medication.

4.3.3.3. Probability of existing users continuing to receive prescriptions for opioid medicines

The probability of continuing to receive prescription for opioid medicines from first prescription in 2009 until end of follow up was calculated using a permitted gap size of 90 days between the end of a prescription and the start of the next for existing users of opioid medication. Death was treated as a competing risk. This analysis was conducted to provide a point estimate of the likelihood of having had a gap for any patient who had an opioid prescription in the past 6 months.

4.3.3.3.1. Subgroup analysis based on length of continuous receipt of opioid medicine before first prescription in 2009

Patients were stratified by length of usage of opioids prior to 2009 (Section 3.3.4.11) and the probability of having had a gap in opioid medication from first prescription in 2009 until end of follow up was calculated. This analysis used a gap size of 90 days between the end of a prescription and the start of the next for existing users of opioid medication. Death was treated as an interruption as only probability of continuation was plotted. This was to test the hypothesis that the length of time patients using opioid medicine before their first prescription increases the likelihood that they continue receiving prescriptions for opioid medicine usage after 2009.

4.3.3.4. Comparison of factors that may affect length of treatment in all new patients and long-term new patients

In the previous analysis in this chapter, it was shown that at around 1.5-2 years the rate of patient having a gap in opioid medication slowed so that patients were less likely to have a gap in opioid medication after this time period.

This analysis compared the characteristics of patients in all new users and new users who go on to be prescribed opioid medicines for more than two years. Numbers and percentages

of patients in each category are presented. This was to highlight the differences between the cohorts and also to show what types of patients were long-term opioid medicine users.

4.3.4. Time to interruption in patients receiving opioids for two years or more and the effect of characteristics on rate of time to interruption

Patients were included in this analysis if they had received prescriptions for 2 years without a 90 day gap between the end of prescriptions and the next prescription. Cox regression was conducted to see what baseline characteristics influenced the probability of continuation from after 2 years of treatment. All variables were included in the adjusted model except anxiety and depression as it was anticipated that this variable would be correlated with prescription of an antidepressant.

Patients were only included in this analysis if they had a Townsend score. The proportional hazards assumption was checked using Schoenfeld residuals and by checking that time varying coefficients were insignificant in the multivariate analysis. Hazard ratios and 95% confidence intervals are presented.

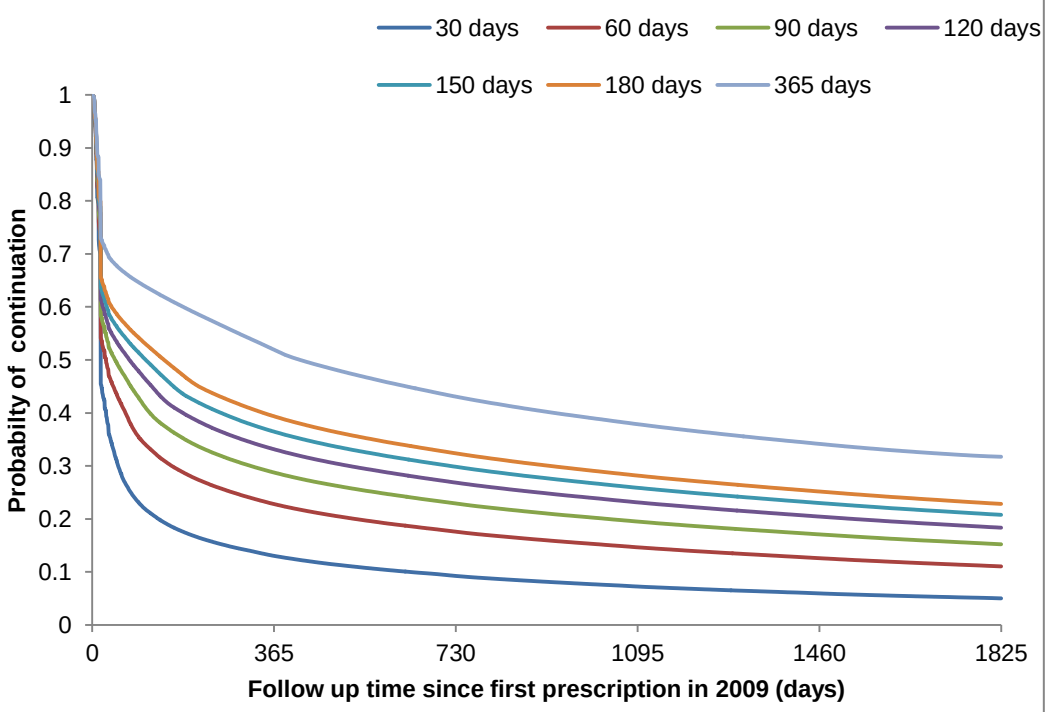
4.4. Results

4.4.1. The effect of varying gap size on the proportion of patients who continue to receive prescriptions for opioid medicines over time

The gap size permitted is a major factor in the probability of continuation. If a gap size of 30 days is permitted, only 5% of patients continue use until the end of the fifth year, in comparison to 11% when a 60 day gap, 15% when a 90 day gap and 23% when a 180 day gap is permitted (Figure 4).

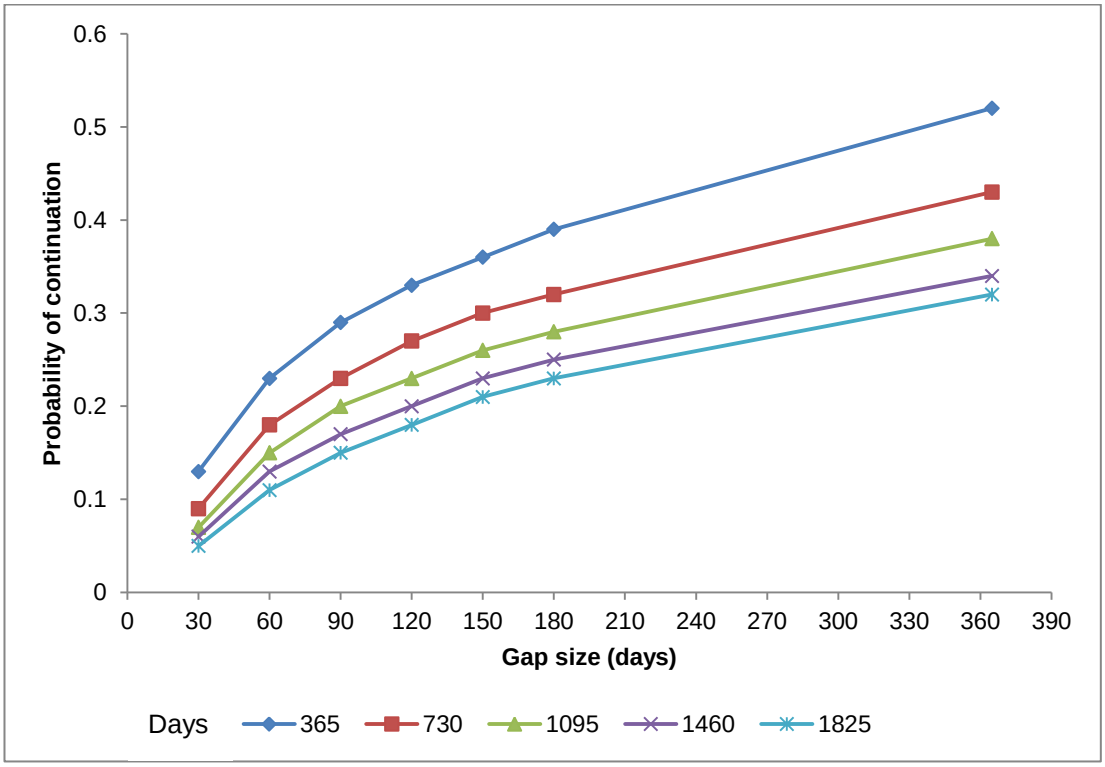
The effect of gap size on the likelihood of interruption reduces as the gap size increases. At around 90-120 days, the relationship between the proportion that remain and the gap size becomes approximately linear. The proportion of patients continuing rises rapidly for smaller gap sizes (Figure 4, Figure 5).

Figure 4 Probability of opioid medicine users continuing to be prescribed opioid medicines when the permitted gap size between prescriptions is varied



Time (days)	365	730	1095	1460	1825
Gap size (days)					
30	0.13	0.09	0.07	0.06	0.05
60	0.23	0.18	0.15	0.13	0.11
90	0.29	0.23	0.20	0.17	0.15
120	0.33	0.27	0.23	0.20	0.18
150	0.36	0.30	0.26	0.23	0.21
180	0.39	0.32	0.28	0.25	0.23
365	0.52	0.43	0.38	0.34	0.32

Figure 5 Probability of continuing to receive prescriptions for opioid medicines at the end of each year of the study, using gap size as the independent variable

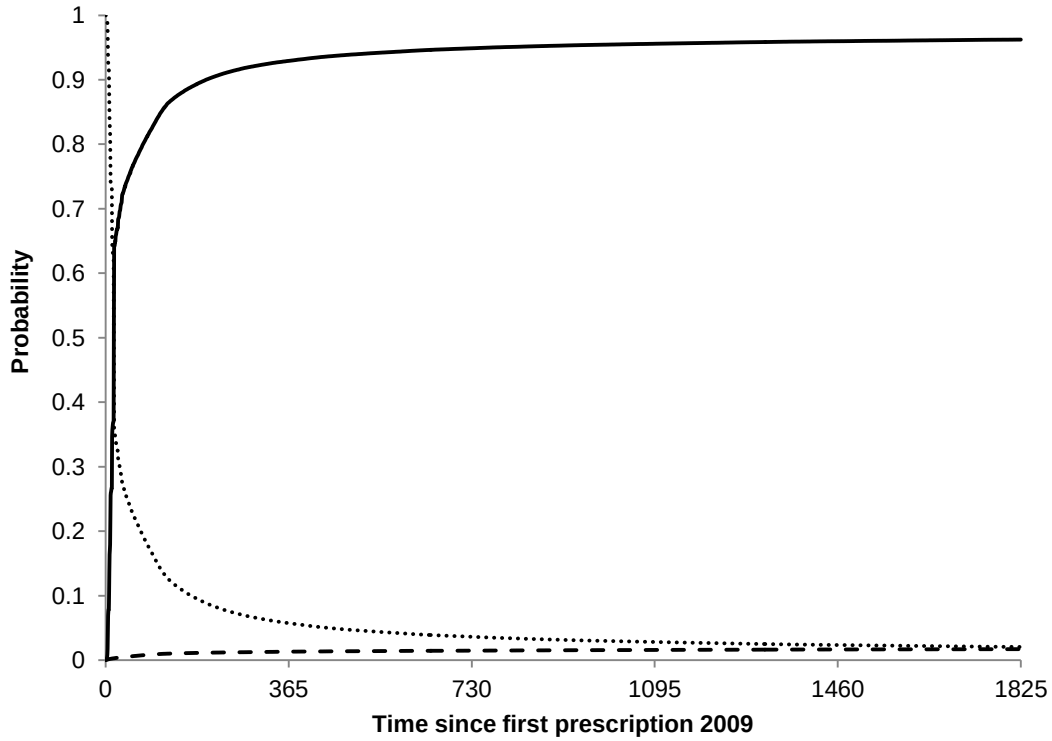


4.4.2. Probability of new users continuing to receive prescriptions for opioid medicines

Almost two thirds of patients have a gap in opioid prescriptions after their first prescription within 5 years. In fact, 65% of patients interrupt treatment after the first 17 days. Only 5.75% of patients continue after one year. After Year Two, the rate of discontinuation continues to slow and of the patients who reach two years, 56.59% continue until the end of the study. Only 2.06% of patients who started opioid medicine in 2009 continuously received medicines until the end of the five year period (Figure 6).

Only a small proportion of patients die by the end of the study (1.7%), with the probability of dying greatest at the very start of the study (Figure 6).

Figure 6 Probability of new users of opioid medicines continuing to receive prescriptions for opioid medicines during the five year study period



Time (days)	365	730	1095	1460	1825
Patients at risk	14,357	8,333	6,031	4,545	3321
Continuation	0.0575	0.0364	0.0283	0.0236	0.0206
Death	0.0132	0.0148	0.0159	0.0167	0.0171
Interruption	0.9292	0.9488	0.9558	0.9598	0.9623

4.4.2.1. Probability of new users continuing to receive prescriptions for opioid medicines: subgroup analysis of patients with 3 or more prescriptions in first 91 days of follow up

When including only the patients with a least three prescriptions in their first quarter in the time to interruption in treatment analysis, a large proportion of patients still have a gap in receiving opioid prescriptions in what remains of their first year (Figure 7). However, the proportion that discontinue in the first year is smaller in this group of patients: 30.9% are still

receiving an opioid at the end of the first year whilst when including all patients in the analysis and not just patients with 3 prescriptions in the first quarter, 5.8% are still remaining at the end of the first year (Table 17).

In the first two years, 79.7% of the patients have had a gap in opioid medication whilst 96.4% of patients in the all patient analysis had had a gap in opioid prescriptions (Table 17).

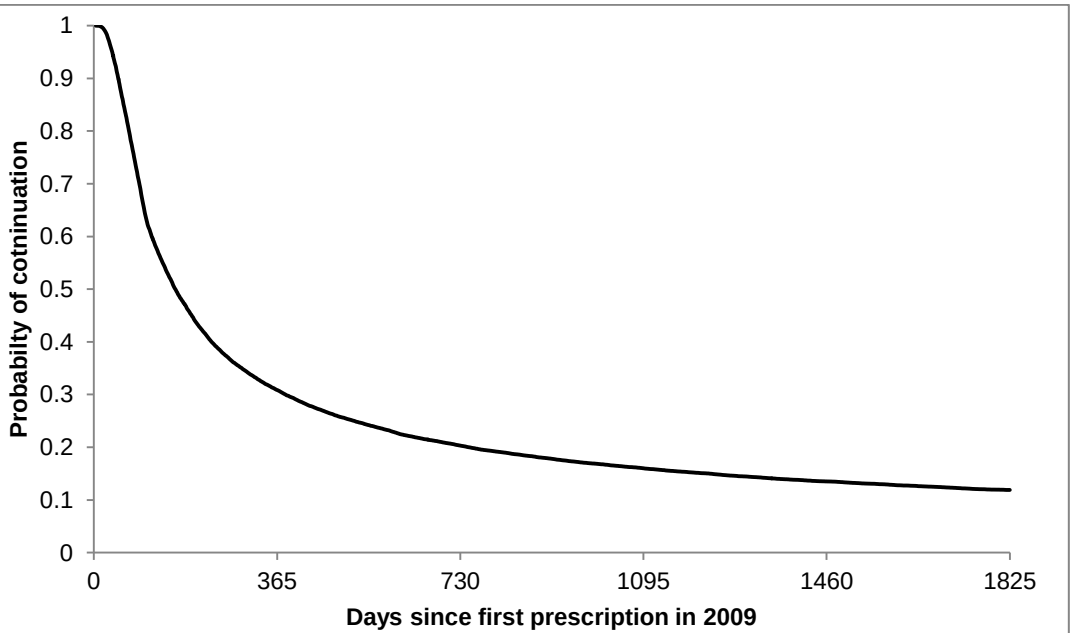
However, of the patients who were continuously prescribed opioid prescriptions until the end of the second year, 58.6% in the 3 prescriptions in the first 90 day analysis group have discontinued by the end of the 5th year. This is similar to the all patients analysis in which 56.6% patients continue receiving prescriptions until the end of the 5th year (Table 17).

The proportion that remained at 5 years was 11.9% (Figure 7).

Table 17 Probability of continuation in prescribing of opioid medicines, in all new opioid medicines users, compared to the subgroup of users with three prescriptions in the first 91 days

Number of days since 1st prescription 2009	**Probability of continuing to receive opioid medicine prescriptions (without a gap) until the end of time period**	
	All new opioid medicine users	Patients with ≥3 opioid prescriptions in 1st 91 days of follow up
365	0.058	0.309
730	0.036	0.203
1095	0.028	0.160
1460	0.024	0.135
1825	0.021	0.119
Proportion of patients who were still receiving prescriptions at 2 years receiving prescriptions at 5 years	0.566	0.586

Figure 7 Probability of new users of opioid medicines continuing to receive prescriptions for opioid medicines during the five year study period, subgroup analysis of patients with three or more prescriptions in the first 91 days of follow up

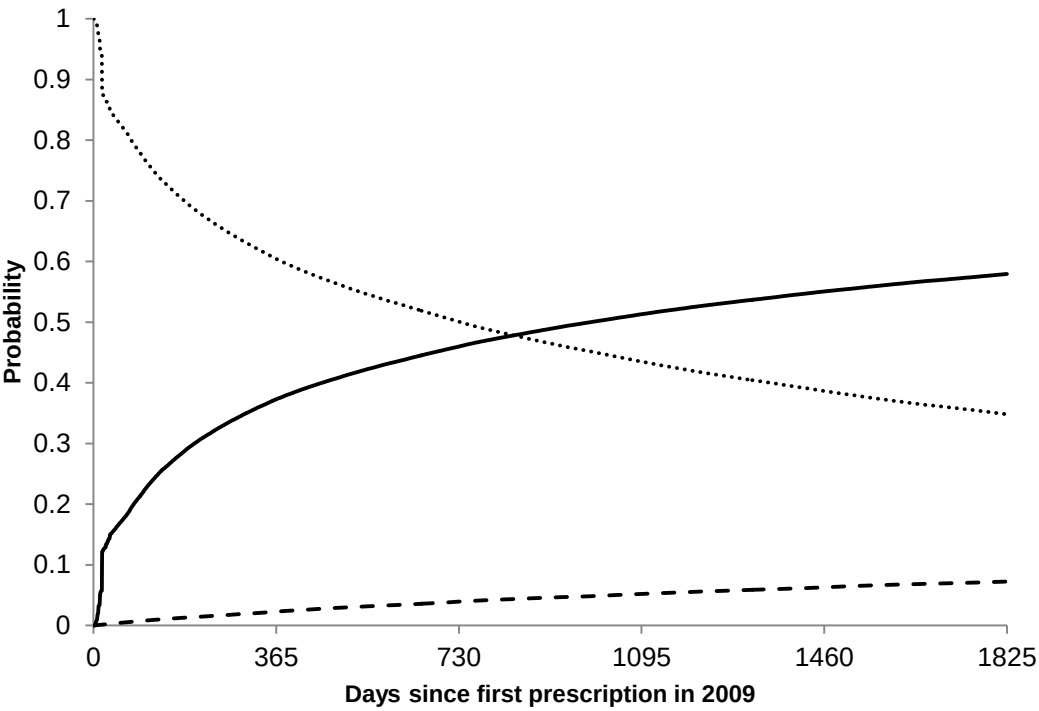


Time (days)	365	730	1095	1460	1825
Patients at risk	9692	5875	4315	3289	2437
Probability of continuation	0.308664	0.203128	0.1601	0.1352	0.1190

4.4.3. Probability of existing users continuing to receive prescriptions for opioid medicines

There is an initial sharp decrease in the proportion of existing users continuing to receive opioid medicines, this is up until day 17. This is similar to the pattern seen in the new opioid medicine users. At 5 years, just over a third of patients (34.82%) continue receiving prescriptions for opioid medication (Figure 8). The risk of death at the end of the five year period is higher in the group of existing opioid users than in the new opioid users (7.2% in the existing group v 1.7% in the new group).

Figure 8 Probability of existing users of opioid medicines continuing to receive prescriptions for opioid medicines during the five year study period

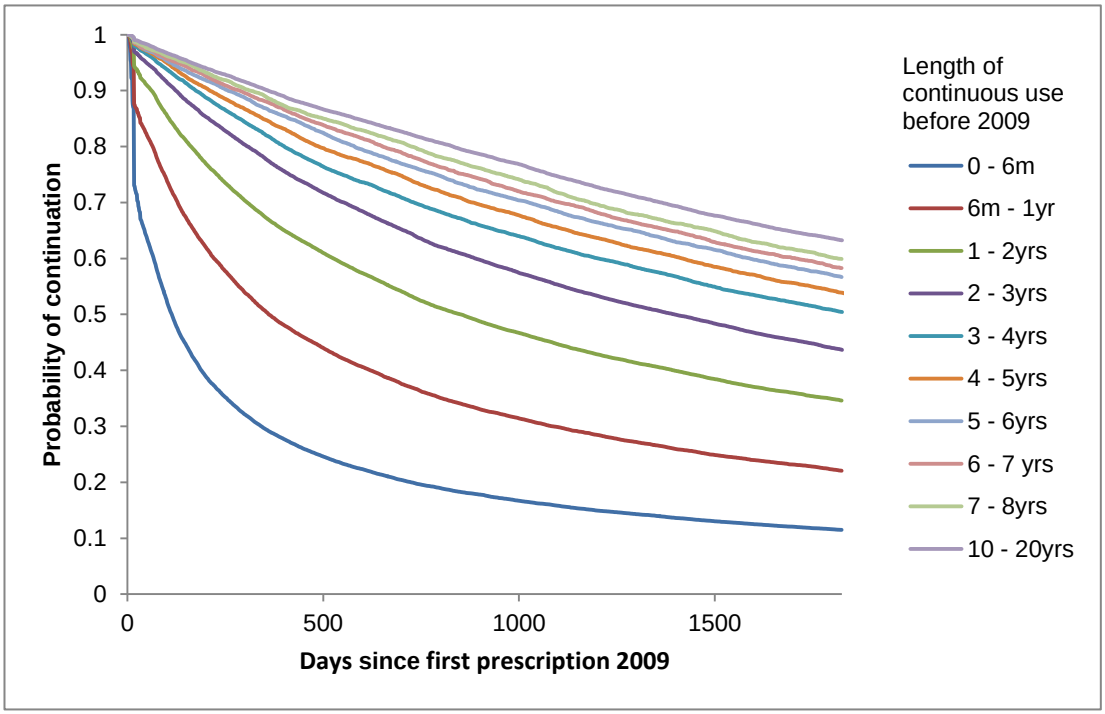


Time (days)	365	730	1095	1460	1825
Patients at risk	116,248	90,294	73,018	61,400	48,881
Continuation	0.6043	0.5008	0.4349	0.3865	0.3482
Death	0.0229	0.0394	0.0520	0.0630	0.0724
Interruption	0.3728	0.4598	0.5131	0.5505	0.5793

4.4.4. Probability of existing users continuing to receive prescriptions for opioid medicines: subgroup analysis by time receiving opioid prescriptions before 2009

For shorter times on opioids, the shape of the graph is similar to new opioid medicine users. However, the graph becomes more linear the longer patients have been receiving continuous prescriptions for opioids (Figure 9). In the groups of patients that have been using opioids without a gap for greater than two years, the initial drop in patients continuing usage is lost (Figure 9).

Figure 9 Probability of existing users of opioid medicines continuing to receive prescriptions for opioid medicines during the five year study period, stratified by length of continuous use before 2009



Patients using medication for longer before 2009 were more likely to continue using opioid medication after 2009. Almost two thirds of the patients who had been receiving prescriptions for opioids for the past 10-20 years continued use until the end of the five year period. This is compared to only 11.49% of the patients who have been receiving prescriptions for only 0-6 months before 2009 in the cohort (Figure 9).

4.4.4.1. Demographic, comorbidities and drug types characteristics of all new opioid medicine users in comparison to patients who have received continuous opioid prescriptions for 2 years

Of the 290,296 new opioid users, 8,258 patients were still receiving prescriptions for opioids two years after the start of their use. The majority of the patients receiving opioid prescriptions for 2 years were women (60.95%), which is similar to the new user cohort (59.59%). In terms of age, the two years patients tended to be older where the largest

category is over the age of 65 (42.46% 65 and over). This is in contrast to the new user cohort where the majority of patients are in the youngest category (43.02% 18-49yrs) (Table 18).

The patients receiving opioids for two years tend to have more comorbidities than the new users. Two thirds (64.34%) of patients receiving prescriptions for opioids for two years had at least one comorbidity. However, only 15.5% had more than three comorbidities. In comparison, in the new opioid medicine user cohort, patients had fewer comorbidities, with half (50.32%) of patients having no comorbidities and only 10.37% having more than three comorbidities (Table 18).

Over half of patients (59.46%) who had received opioids prescriptions for at least 2 years had had a Read Code for anxiety or depression at some point in their record. For the majority of patients, this was before they were prescribed an opioid. Fewer patients (51.04%) in the new opioid user cohort had been coded as anxious or depressed at some point in their record (Table 18).

A high proportion of patients using opioids for 2 years had received an antidepressant before their first prescription in 2009. A quarter of patients (26.94%) had had an antidepressant (non TCA, non duloxetine) in the year before or after opioid treatment in the patients using opioids continuously for two years, whilst one in five (18.54%) patients in the new opioid user cohort had received an antidepressant prescription in the year before or after (non TCA, non duloxetine) (Table 18).

One in five patients (21.16%) in the long-term group received a prescription for a benzodiazepine or other anti-anxiety drug in the year before or after opioid treatment started. This is in comparison to only 16.21% in the new opioid user cohort (Table 18).

Table 18 Characteristics of new opioid user cohort and the subgroup of patients that receive opioid medicines for greater than 2 years

Characteristic	New opioid user cohort (n=290, 296) (%)	Patients receiving opioids for 2 years (n=8,258) (%)
Age group (Years) 2009		
18-49	124,876 (43.02)	2,104 (25.48)
50-64	76,716 (26.43)	2,648 (32.07)
65+	88,704 (30.56)	3,506 (42.46)
Gender		
Male	117,317 (40.41)	3,225 (39.05)
Female	172,979 (59.59)	5,033 (60.95)
Townsend score		
1	35,296 (20.42)	821 (17.36)
2	37,033 (21.42)	927 (19.61)
3	36,479 (21.1)	1,054 (22.29)
4	37,353 (21.61)	1,061 (22.44)
5	26,714 (15.45)	865 (18.3)
Missing (%) of total	117,421(40.45)	3,530 (42.75)
Co-morbidities before 1st opioid prescription		
0	146,067 (50.32)	2,945 (35.66)
1	78,611 (27.08)	2,462 (29.81)
2	35,501 (12.23)	1,571 (19.02)
>3	30,117 (10.37)	1,280 (15.5)

Characteristic	New opioid user cohort (n=290, 296) (%)	Patients receiving opioids for 2 years (n=8,258) (%)
Read coded at any point in the data with depressed or anxious diagnosis or symptoms		
None	142,120 (48.96)	3,348 (40.54)
before opioid started	126,083 (43.43)	4,207 (50.94)
after opioid started	22,093 (7.61)	703 (8.51)
Antidepressant prescribed in year either side start date of opioid		
None	236,469 (81.46)	6,033 (73.06)
Yr. before opioid started	40,562 (13.97)	1,746 (21.14)
Yr. after opioid started	13,265 (4.57)	479 (5.8)
Benzodiazepine/ anti-anxiety drug prescribed in year either side start date of opioid		
No	243,251 (83.79)	6,511 (78.84)
Yes	47,045 (16.21)	1,747 (21.16)
Number of patients with fewer than 3 prescriptions in first quarter	N/A	2,353 (28.49)

4.4.5. Analysis of characteristics associated with change in rates of time to gap in prescriptions of opioids in the cohort of patients using opioids for at least 2 years

4.4.5.1. Univariate analysis

In the univariate analysis, patients who were 65 years and older discontinued after 2 years of continuous use at a faster rate than those in the youngest category. Women were also more likely to discontinue at a slower rate than men. Patients with greater than 3 co-morbidities

were also more likely to discontinue at a faster rate than those with fewer comorbidities. Although patients who were recorded as anxious or depressed did not discontinue at a significantly faster rate than those who were not Read coded as depressed or anxious, patients who received an antidepressant in the year before opioid use started were found to discontinue at significantly slower rate than those who did not. Patients who received benzodiazepines and/or anti-anxiety drugs in the year before or after the first opioid prescription were also more likely to discontinue at a slower rate (Table 19).

4.4.5.2. Multivariate analysis

When covariates are entered into a multivariate analysis, the covariates which remain associated with a slower rate of discontinuation include younger age group, female gender and receipt of an antidepressant within the year before the start of the use of opioid (Table 19). Having greater than 3 comorbidities and benzodiazepine and/or anti-anxiety drug use are no longer significant.

Table 19 Cox regression time to interruption in patients who had continuously received opioid medicines for 2 years after starting opioid use in 2009

Characteristic	**Univariate analysis**			**Multivariate analysis**		
	HR	LCI	UCI	HR	LCI	UCI
Age group (years)						
18-49	1	1	1	1	1	1
50-64	1.05	0.95	1.16	1.08	0.94	1.25
65+	**1.29**	**1.18**	**1.42**	**1.26**	**1.09**	**1.46**
Gender						
Male	1	1	1	1	1	1
Female	**0.87**	**0.81**	**0.94**	**0.83**	**0.75**	**0.92**
Number of co-morbidities before opioid starts						
0	1	1	1	1	1	1
1	0.99	0.91	1.09	0.90	0.80	1.03
2	1.06	0.96	1.18	0.89	0.77	1.03
>3	**1.16**	**1.04**	**1.29**	1.01	0.86	1.18

Characteristic	Univariate analysis			Multivariate analysis		
Read coded as depressed or anxious						
None	1	1	1	-	-	-
before opioid started	0.93	0.86	1.00	-	-	-
after opioid started	0.94	0.82	1.08	-	-	-
Received an antidepressant						
None	1	1	1	1	1	1
Year before opioid started	**0.84**	**0.77**	**0.92**	**0.83**	**0.73**	**0.95**
Year after opioid started	0.88	0.75	1.04	0.86	0.68	1.09
Received a benzodiazepine in year before or after opioid starts						
No	1	1	1	1	1	1
Yes	**0.83**	**0.76**	**0.91**	0.90	0.79	1.03
Townsend comorbidity score quintile						
1	1	1	1	1	1	1
2	0.92	0.78	1.08	0.94	0.79	1.10
3	0.97	0.83	1.14	1.00	0.86	1.17
4	0.90	0.77	1.05	0.93	0.80	1.09
5	0.90	0.76	1.06	0.95	0.81	1.12

NB A hazard ratio of less than one indicates that a particular group discontinued at a slower rate than the reference group, i.e. they continue to take opioids for longer. Figures shown in bold are significant, antidepressant Read Codes were not entered into the multivariate analysis as it is likely they are highly correlated with receipt of antidepressant prescription

4.5. Discussion

4.5.1. Effect of varying the permitted gap size between prescriptions on the probability of continuing to receive opioid medicines

Three times as many patients continued receiving opioid prescriptions continuously until five years when a 90-day gap was permitted compared with a 30-day gap. This large difference suggests that there are substantial periods between opioid prescriptions for some patients taking opioids. The relationship between gap size and proportion of patients continuing became approximately linear at a gap size of between 90-120 days. For a linear relationship, during each 30 day increase there must be the same change in the number of patients having a gap, and so this may indicate that the gap size is no longer related to the time from the previous prescription and potentially may relate to the probability of starting a new episode of opioid medicine use.

Patients may have gaps in their prescription record for a number of reasons (1) obtaining supplies from somewhere else other than their GP e.g. going in to hospital and receiving medication there, (2) building up an excess of medication (e.g. by ordering before the previous prescription has expired) and taking it at a later date, (3) taking the medication at a lower dosage than is prescribed and thus extending the length of the original prescription and (4) the patient stops taking the medication completely and then starts again.

In the first three instances the patient continues to take the medicine despite having a gap. The probability that a patient has indeed stopped taking the medicine increases as the gap size increases as it becomes less likely that the patient would be able to obtain adequate supplies to fill the gap. The ideal gap size used in a study to measure persistence will retain only the patients that are continuously taking opioid medicine. However, as this cannot be determined from the data a gap size of 90 days was used as the definition of an interruption as this strikes a balance between retaining patients that are likely to be continuing previous opioid medicine and those randomly starting to receive prescriptions for opioid medicines

again. Note that unless a small gap size was used it is not expected that there will be any drastic changes in the results due to the smooth and gradual change with gap size.

4.5.2. Proportion of patients that continue opioid medicine and how probability of continuation changes over time

The prevalence of opioid use for non-cancer pain in the population is high with 10.58% of the U.K. population using opioids at some point in the year 2009 (Section 3.5). However, only a small proportion of new users of opioid medicines appear to use opioids continuously for long-periods. The probability of a patient receiving continuous opioid prescriptions (with no 90-day gap) for the full 5 year study period is only 2.06%. Nevertheless, as the number of patients that were first prescribed opioids (290,296 incident patients in 2009) is large this still amounts to a significant number of patients when the probability of continuation is translated up the numbers of patients in the U.K. population. Over time the number of patients taking opioids each year accumulates and in 2009 205,216 existing patients were recorded as receiving prescriptions for opioids.

As the data shows, the probability of a patient continuing in the existing opioid medicine user group is related to the length of time they have been taking opioids prior to the study start, a third of these patients will continue to use opioids for the next five years in addition to the time before they entered the study. This may be extremely long periods for many patients (Figure 9).

As the length of time a patient continues to receive prescriptions for opioid medication is related to the length of time they previously used opioid medication, one of the objectives of this study was to see at what point patients are more likely to continue opioids use. This time point may serve as a clinical check point for prescribers to ensure there is a documented future plan and that the patient has a definite improvement in quality of life as a result of taking opioids.

In the group of new opioid medicine users, in their first year of use most patients appear to interrupt (i.e. have a gap in treatment), with 93% interrupting in the first year. In subsequent years far fewer patients discontinue with almost two thirds of patients that continue for the first year also continuing into the second year and three quarters of patients continuing from their second year into the third year. Of the patients that continue to the second year 56.59% of the patients continue until the end of the 5 years.

When the existing opioid users are analysed using the same time to gap in prescriptions, stratified by length of use before, it can be clearly seen how the probability of stopping decreases with increasing time receiving continuous prescriptions of opioids. In particular the sharp drop off at the start is mostly gone by the 2-3 year group. The lines also become straighter with increasing time before indicating that the rate of discontinuation is becoming constant in time. The cut of point of 2 years was used as long term use in further analysis as by this time the initial drop off point is small.

A recent study using health insurance claims from a nationally representative sample, [198] that examined the probability of continuation in commercially insured patients in the U.S.A similarly found that 5.3% of patients continued taking opioid medication at 1 year. The study included patients with many initial potential indications. This is similar to the results found in this study. This is perhaps surprising given the fact that the U.S.A. has a much higher rate of prescribing per head than the U.K. however in the U.S.A. [14] it was found that most of the opioid consumptions in the U.S. occurs in a small number of patients and in one commercially insured population 5% of patients accounted for 70% of use [202]. This may mean the remaining patients who start opioid medicines use these medicines for only a short period of time, patients are receiving higher dosages or more patients start medicines for indications they would not in the U.K..

In other U.S.A. based studies that use a similar method of time to discontinuation but in patients that had at least 90 days of treatment, much higher proportions of patients continue opioid medicines. In one such study 92.52% of patients in one study of veterans heath

records (n=550,616) continued opioid use for at least one year [97] whilst 67% of patients in a privately insured population continued to receive opioids for 5 years [96]. This is a far larger proportion when comparing to the likelihood of continuation using the U.K. data and when compared to the proportion of patients with three prescriptions (which may equate in some cases to 90 days of use) that continue still far higher. However, these studies did not differentiate between new and existing populations and so are likely to provide much higher proportions of continuing patients. Thus there is a great variation in the probability of continuation in the U.S. population.

In a U.K. study including patients that had musculoskeletal conditions (using CPRD data), Bedson [1] reported the proportion of patients who had had 3 prescriptions that continued to receive opioid prescriptions. This analysis showed that approximately 40% of new opioid medicine users continued opioid medication for at least one year after and with approximately 30% of patients continuing for at least 2 years and that these proportions were stable when cohorts were extracted each year from 2002 until 2011. In the current study when patients with a least 3 prescriptions were studied approximately 30% and 20% continued use for a least one and 2 years respectively. A reason for this difference is likely to be due to the fact Bedson et al. used a permitted gap size of 180 days and so it would be expected that higher proportions of patients would be found to continue (Figure 4).

Other studies have used different methods of measuring persistence with opioid medicine and also include only certain types of drug. This makes direct comparisons of continuation difficult. For example, a study in Norway using dispensing data [175] found that 67% of patients who received 2 strong opioid prescriptions within the first 70 days of treatment continued to receive at least one prescription in the next year. However, the study included only strong opioid patients who may be more likely to continue taking medication and the study only required patients to receive one prescription per year in comparison to continuous use. Therefore, the study counted patients that receive intermittent prescriptions of opioid medication as long-term users and had a minimum threshold of two prescriptions.

The study in this chapter showed that there was a large drop at 17 days. This corresponds to the length of a prescription for 100 codeine tablets where the prescribing direction is 'One or two tablets four times a day'. This is a common prescription type and implies that a large proportion of patients only have one prescription for opioid medicine.

Over a quarter (28.53%) of patients that received opioid prescriptions for greater than 2 years were found to have less than 3 prescriptions in their first quarter. As studies that analyse opioid use usually include only new users of opioid medicines these patients (that continue despite having less than 3 prescriptions in their first quarter) would be excluded from further analysis. It could be possible that prescribers are reluctant to frequently issue prescriptions to certain patients at the start of treatment so this could possible exclude patients that may continue receiving opioid prescriptions. Also, patients are still likely to discontinue opioid use in the months after the first 90 day period. This means that the 3 prescription / 90 day cut off point may include patients that are likely to discontinue in the next few months and therefore, depending upon the research question, a longer period of time may be appropriate.

4.5.3. Characteristics that affect likelihood of continuing to be prescribed opioid medicines

This study identified that patients who were younger, were women or were depressed before they started opioid use were more likely to continue long-term opioids (Table 19).

Younger patients who had continuously used opioids for 2 years were more likely to continue opioid medication until the end of the study. In this study and in other cross sectional studies in the U.K. [2, 27] a higher proportion of patients that are older are found to be receiving prescriptions for opioid medication. Cross sectional studies are an amalgamation of the new patients taking opioid medication at one point in time and the existing patients who have been taking opioids for a while. The study in this chapter shows that although a greater number of older people are prescribed opioids initially, younger patients are more likely to continue using opioid medication past the 2 year point. This has implications for patients as

younger patients have the potential to continue this medication for many years. Also of concern is the fact that these women are of child bearing age. There has been an increase in the number of babies born with opioid withdrawal in the U.S.A. due to the increased use of opioids in the U.S.A. [203]. Whilst the dosages of opioids used and types of opioids used are likely to be different in the U.S.A. [14], further work is required to understand whether this is an issue of concern in the U.K. For example the fact that a woman is taking opioid medicines may affect her quality of life as she may choose to avoid having children whilst taking the medicine.

This study looked at time to interruption of opioid medicines in patients that had been receiving opioid medicines for at least 2 years. Before the cox regression was conducted in only patients that were taking opioids for greater than 2 years, a cox regression model was performed that included all the patients. However, in this model the proportional hazards assumption was violated. This was because at the start of opioid therapy older patients were found to be more likely to continue opioid use whilst younger more likely to interrupt their treatment however after approximately 2 years this relationship was reversed with younger patients more likely to continue to be prescribed opioid medicines. At the start of treatment this may reflect the fact that older patients are more likely to have chronic pain conditions than younger patients, however the reasons younger patients continue to take opioid medicines after this are likely to be different.

Older patients may be more accepting of pain and therefore more likely to manage their pain without higher dosages of medication. Indeed an Australian study that looked at the characteristics of patients prescribed strong opioids for at least 6 weeks [110] found a marked difference in the characteristics of patients based upon age groupings. Older patients taking opioids were less likely to have sleep problems, poor health, lower pain severity, lower pain interference scores and better self-efficacy scores. This may reflect that GPs may have a lower threshold for prescribing opioids to older patients, however, it could also be an indication that patients are more likely to cope with their pain better in older age. In another study that looked at the reason why patients over the age of 45 years were more

likely to discontinue opioid therapy (U.S.A., n=1,477) [204] patients were most likely to discontinue opioid use because “they preferred to manage their pain without the using strong pain medicines”. Although there is no data regarding preferences in younger patients, older patients may potentially be more inclined to stop opioid medicines when they feel they do not need it anymore. Further work should be conducted into the reasons why younger patients continue to be prescribed opioid medicines. For example whether older patients may be more likely to look for alternative treatments, whether older patients experience more adverse events or whether it is just because younger patients are prescribed opioids for conditions that last longer. This would be with the aim of identifying if patients quality of life is better off with or without the use of these medicines or whether certain strategies to manage pain could be explored in younger patients.

Patients who were depressed before they started opioid treatment were found to be more likely to continue long-term opioid medication. This result provides evidence that in the U.K. a history of psychological comorbidity (treated with antidepressants) is associated with a greater probability of long-term use. This has not been shown previously in the U.K. except for a regional study of patients with joint pain [91]. As discussed in (Section 2.9.4) this is a sign of adverse selection.

The relationship between depression and chronic pain is complex. In cross sectional studies and some cohort studies it is impossible to know if the patient had depression first or that being in chronic pain was causing the depression or whether opioid use was the cause of the depression. This study included a marker of depression prior to opioid use because this provides some evidence that history of depression is associated with long-term opioid use and it is not just the depression developing after opioid treatment has started.

As there are so many factors that affect whether a patient persists with medication it is difficult from this study to see what may be really dominating the way in which opioids are used in this country. However as this analysis of characteristics of patients included patients that had been using opioids for at least two years it may be assumed that they at least

benefited from treatment at the start of the study and that the side effects at opioid initiation did not preclude use for the two year period. Potentially changes in treatment or dosage which increase the likelihood of side effects may be the reason for stopping use, alternatively certain patient groups may be treated in different ways or potentially patients may be self-selecting for long-term treatment. Further work could be undertaken to examine these factors. However a finding from this study is that young patients, women and those patients with depression have been found to continue opioid medication in the long-term.

4.5.4. Strengths and limitations

This study used a competing risks method to determine the probability of patients continuing opioid use over a five-year period. This study included all patients receiving any sort of opioid.

This study only followed patients over their first episode of opioid use, it is likely that many patients may start opioid use again and potentially become long-term patients thus this study may underestimate the proportion of patients that use opioids long-term. Additionally, prescribing patterns may be different in patients who restart opioid medication.

This study only measured continuation of opioids and did not differentiate between dosages used. Other studies have found that the dosage prescribed is linked to the probability of continuation of opioids. It may be that, due to the large proportion of patients taking lower dosages of opioid medicines that the characteristics of the patients using weaker opioids predominate. In the next chapter the probability of increasing dosage and the probability of long-term use in patients using higher dosages is analysed. In later chapters the characteristics of patients that receive prescriptions for higher daily dosages of opioid medication and continue to use high dosages of opioids is also analysed.

4.5.5. Summary

This study found that only 2.06% of the new opioid medicine users were continually prescribed opioid medicines for the full five year period of the study. However, due to the fact

such a large proportion of the population use opioids this is still a significant number of patients who continue to receive prescriptions for opioids each year. The length of time patients had been using opioids prior to 2009 was related to the probability that patients would continuously receive opioid prescriptions for the next five years. When including new and existing users of opioid medicines, one in thirty people in the U.K. population who started opioids for non-cancer pain in 2009 were continuously prescribed opioids for a full year

In previous studies 90 days or 3 prescriptions have been used to define long-term use, however in this study patients were still found to be likely to discontinue use in the next few months even after they had received 3 prescriptions. Patients were also likely (28%) to receive fewer than 3 prescriptions in their first quarter when they went on to continue to receive prescriptions for at least 2 years.

When analysing the characteristics that affect the rate of discontinuation after the first two years of use, it was found that young patients, female patients and patients with depression before starting opioid medication were more likely to continue opioid use.

Chapter 5. Estimating dosages of opioid medicines prescribed and predicting time to interruption based on estimated dosages

5.1. Introduction

In this chapter, the dosage prescribed to a patient per day is estimated in the first quarter of 2009 and used as a baseline predictor of the probability of continuation (in the form of time to interruption) in the receipt of opioid medicines in existing users of opioid medicines. In the previous chapter, time to interruption in opioid medication was measured for new and existing users of opioid medicines. The length of time before first opioid prescription was seen (Chapter 4) to be a strong predictor of continued use, therefore this is also included as a predictor in the time to interruption analysis based upon dosage. The effect of dosage has been shown in studies in the U.S. to be an important factor that influences time to interruption [96, 97]. Including the current dosage and length of use before first prescription in 2009 may provide a more accurate prediction of future use of opioid medication and so provide more useful information for people who may use the results of this research.

A secondary outcome of this study is the prevalence of the use of various dosages of opioid medication. In previous studies that report the proportion of patients receiving different dosages, in the U.K., only patients taking strong opioid medicines (excluding tramadol) are included [2, 205]. If patients are taking weak opioids at the same time as the strong opioids then calculation of dosages including only strong opioids will underestimate the dosage consumed. In this chapter, an analysis was undertaken to see by how much the calculated dosage a patient receives is affected by the addition of the weak opioids and tramadol. This showed how addition of weak opioids and tramadol changes the estimated dosage prescribed to patients.

This chapter also reports the number and the types of opioids used by the patients assigned to different dosage groups. There is currently a tremendous range of opioid preparations on the market, some with immediate and modified release preparations, and some with multiple delivery routes and release profiles [23]. Opioid guidelines usually suggest starting dosages of opioid medication and also that opioids can be rotated if the patient suffers adverse events [69]. However, there is little guidance (for example within the “Opioids Aware” initiative [69])

on whether to combine opioids and how best to evaluate the benefit to patients of combinations of opioids. Intuitively, use of multiple opioids by a patient may mean it is difficult for the patient to know what is working (if they are switching between using opioids) and for the prescriber to monitor the patient's opioid consumption (as the prescriber has to calculate the combined oral morphine equivalents OMEQ). The use of multiple opioid types has also been found to be a predictor of misuse [115], possibly because it is more difficult to monitor what the patient is taking if they are receiving multiple prescriptions. Therefore, the number and types of opioid used at various dosage categories is also reported in this chapter to understand whether combinations of opioids medicines are used in common practice and whether the effectiveness of these combinations should be an area for future research.

5.2. Aim and objectives

Aim: To measure the influence of dosage on length of opioid use

The objectives include:

- To identify a method of measuring the dosages of opioid medication prescribed to patients using CPRD data
- To use the method to calculate the proportion of patients prescribed different dosages of opioid medicines
- To present the opioid drugs and drug combinations used at different dosages
- To calculate the probability of continued future use based on the calculated prescribed dosage

5.3. Method

A flow chart of the cohort selection and analyses for Chapters 5 and 6 can be found in Appendix 1.

5.3.1. Study design, data source and cohort

This study is a retrospective cohort study using a cohort of adult opioid medication users without a cancer diagnosis who received a prescription for an opioid medication in 2009 using data from CPRD (Chapter 3). In this chapter, patients were only included if they had at least one quarter of a year of follow up after the first prescription in 2009. This was because their dosage was calculated per whole quarter of follow up time.

All non-cancer patients were included in the initial analysis whilst only existing users of opioid medicines were included in the time to interruption based on length of previous use and current dosage (see Appendix 1).

Patients were followed up through whole quarters of data from their first quarter 2009 until death, leaving the surgery, interruption of opioids or final upload of data to CPRD. Data was extracted in January 2015 and so the maximum follow up time was six years.

5.3.2. Data management

5.3.2.1. Duplicate management

Prescriptions that were issued on the same day for the same product name and form, quantity, strength and dose were removed. This is because it is assumed that it is more likely to be an administrative error than for a patient to require a prescription for an identical item on the same day.

5.3.2.2. Outlying quantities

Outlying quantities were identified if the quantity exceeded 90 days of treatment for schedule 2 and 3 opioids (though this excluded tramadol), 180 days for all other opioids or were a

quantity of 0. They were then replaced with the median number of dosage units for the same opioid drug type and route of administration.

5.3.3. Outcome measures

5.3.3.1. Rationale for method of calculating opioid medicine dosage

Dosages were calculated by summing the total amount of OMEQ that were prescribed within a 91 day period and dividing this by 91 days. This is an estimated measure of opioid consumption. Ideally, the actual daily dosage that a patient consumes would be used in further analyses. However, as with most database based epidemiological studies, it is not possible to know from what the patient is prescribed what is dispensed and what is actually taken. The daily dose as interpreted from the prescription (ndd) could be used to estimate the dosage consumed. However, in the case of opioid medication, because daily dosages may be missing as the patient is prescribed medication “as required” and the patient can potentially be taking multiple opioids and multiple preparations of the same opioid, the daily dosage (ndd) may not be representative of what the patient actually takes. In studies that use daily dosage on the prescription, the amount per day can be summed using the daily dosage on various prescriptions (e.g. morphine sulphate 10mg twice daily and morphine sulphate 30mg twice daily could be summed to 40mg twice daily). However, if a patient is using multiple opioid drugs, strengths and/or opioids with different release profiles, it is difficult to make a judgement as to what the patient is likely to be taking. An additional problem is that, if a patient was allowed to order more medication from their surgery within a specific time frame, the dosage on the prescription would not be representative of what they have taken, as they may be using more than the dosage written on the prescription. This may be more likely with opioid medication than other medications, such as antihypertensive medication, because of the misuse potential of opioid medicines.

5.3.3.2. Method of calculating opioid medicine dosage

5.3.3.2.1. Quarters

All opioid prescriptions prescribed to each patient were divided into quarter time periods by calculating the number of days since the first prescription in 2009 and dividing this time by the number of days per quarter (91 days) to work out which quarter a particular prescription could be attributed to (using the first prescription in 2009 as the start of the quarter period).

5.3.3.2.2. Sum of Oral Morphine Equivalents (OMEQ)

The total OMEQ on the prescription was calculated by multiplying the quantity of dose units on the prescription by the strength of the dose units on the prescription and then multiplying this amount by a conversion factor for each type and route of delivery (Table 20) [25, 206-208]. If a conversion was not available for a particular opioid, the patient was excluded (see Appendix 1). The total OMEQ for the each quarter period was calculated by summing the total OMEQ on the prescription within each quarter for each patient.

Table 20 Oral Morphine Equivalent conversion factors used in this thesis

Opioid drug type	Route of delivery	Equianalgesic ratio
buprenorphine	transdermal	110
buprenorphine	sublingual	50
codeine	oral	0.1
dextropropoxyphene	oral	0.15
dihydrocodeine	oral	0.13
dipipanone	oral	0.5
fentanyl	sublingual	50
fentanyl	buccal	50
fentanyl	transdermal	100
hydromorphone	oral	6
meptazinol	oral	0.04
morphine	oral	1
oxycodone	oral	1.5
pethidine	oral	0.1
tapentadol	oral	0.35
tramadol	oral	0.2

5.3.3.2.3. Length of prescriptions

The length of the prescription was calculated by dividing the total quantity of medication on the prescription by the amount of medication used per day. This was done by using the numerical daily dose (ndd) if present. If no ndd was present, the median length of prescriptions having an ndd for the same opioid drug and route of delivery (e.g. buprenorphine patches or co-codamol tablets) and quantity was used. If no other prescriptions for the same quantity and opioid drug and route of delivery had an ndd, the median length of prescriptions from the same opioid drug and route of delivery was used. By

dividing the amount of OMEQ on the prescription by the number of days on the prescription, the amount per day was calculated. The amount per day was only used to calculate the amount to be passed over to the next quarter.

5.3.3.2.4. Assigning OMEQ from prescriptions that overlap two quarters

For prescriptions that crossed the boundary of a quarter, the dosage for that prescription was split between the two quarters. The amount of OMEQ to subtract was calculated by multiplying the amount per day by the number of days on the prescription that were predicted to be taken after the 91 day interval. The subtracted amount was passed on to the next quarter and any OMEQs from the previous quarter passed on to the subsequent quarter as this is the quarter in which it is assumed the patient took the medication. The total OMEQ per quarter (minus any carry over and plus any OMEQ from the quarter before) was divided by 91 to estimate the dosage per day for each quarter for each patient.

5.3.3.3. Number and potency of opioid medicines prescribed

The opioid drug type that the prescription was for was identified from the product name on the prescription (e.g. morphine, codeine). The number of opioid drug types per patient in the first quarter of 2009 was calculated.

The potency of all the drugs prescribed in the first quarter of 2009 (weak, tramadol, weak and tramadol, strong, strong and weak, strong and tramadol) was also determined. The release profile of the opioid medicine was also determined. Opioids were deemed to be immediate release if they had a maximal duration of 4-6 hrs whilst long-acting opioids were those that were designed to release drug over a minimum of a 12 hr period.

5.3.3.4. Time to interruption (probability of continuing to receive opioid medicine prescriptions)

The time to gap in prescriptions was calculated for each patient as described in Section 4.3.2.4.

5.3.4. Data analysis

5.3.4.1. Dosages prescribed to patients in their first quarter 2009 including and excluding weak opioids and tramadol

For all patients that had both a strong and weak opioid and/or tramadol in their first quarter 2009, the dosage was calculated including and excluding the weak opioids and/or tramadol. The proportion (percentage) of patients within each OMEQ/day dosage category (<50mg, 50-99mg, 100-149mg, 150-199mg , ≥200mg) before and after the addition of the weak opioids and/or tramadol was calculated. These dosage categories were chosen in order to allow comparison with previous opioid studies that looked at the prevalence of dosages used and the risks of overdose associated with certain dosages [163-165]. The proportion (percentage) of patients who had received over 120mg OMEQ/day was also reported as this was the highest recommended dose in the U.K. based "Opioids Aware" guidance. [69] The ratio of patients in each dosage group before and after the addition was calculated to show whether a change had occurred and the magnitude of the change within each group.

5.3.4.2. Dosages prescribed to patients including weak opioids and/or tramadol

OMEQ dosages per day for each quarter were divided into 8 groups as follows; 0-9mg, 10-19mg, 20-29mg, 30-49mg, 50-99mg, 100-149mg, 150-199mg, ≥200mg. A separate category of >120mg was also used.

5.3.4.2.1. Dosages received in the first quarter 2009 and the quarter in which the patient received their highest dosage

The proportion (percentage) of the cohort prescribed a particular dosage in the first quarter 2009 was tabulated. In addition to the dosage patients were deemed to have received in the first quarter of 2009, the highest dose they received at any point (in terms of the highest dose quarter) in the subsequent five years was also tabulated. This was to give an impression of how many patients did or did not increase their dosage. This does not take into account the fact that some patients may die or leave their surgery. However, it will provide

an estimation of the proportion of patients that receive high dose medication at some point in treatment to provide an indication of how many patients within the data have high dose.

5.3.4.2.2. Dosage prescribed in the first quarter 2009 to new and existing users of opioid medicines

The proportion (percentage) of the cohort prescribed a particular dosage in the first quarter 2009 was tabulated in sub-groups of new and existing opioid medication users. This was to show likely starting dosages in new patients and the proportions of existing patients already receiving prescriptions for high dosages.

5.3.4.2.3. Drugs used by patients using different dosages

For each dosage category, the number of opioid medicine drug types used (e.g. morphine and codeine would be two drugs), the potency of the drugs used and the release profiles of the drugs used were categorised and reported as proportions (percentages).

The proportion of patients receiving a particular opioid drug type at each dosage was calculated. This was to show what drugs were more likely to be used at certain dosages. The proportion of patients that were using a particular drug as a single agent within a quarter was calculated to see if it was likely a particular drug was used alone or in combination with another drug at a particular dosage.

5.3.4.3. Relationship between probability of continuation and dosage

The probability of patients continuously receiving prescriptions for opioid medicines for 5 years for patients grouped by dosage received in the first quarter of 2009 and the length of use of opioids prior to 2009 (Section 3.3.4.11), was calculated using the method described in Section 4.3.3.

5.4. Results

5.4.1. Dosages calculated for patients taking strong opioid medication including and excluding weak opioid medication

When weak opioids are included in the calculation, all categories except the lowest dose increase. The largest change is seen in the 50-99mg and 100-150mg OMEQ/day category where it increases 1.75 fold. The proportion of patients at higher dosages also increases but at a smaller magnitude. The proportion of patients in the 120mg OMEQ/day category increases by almost half (1.45) (Table 21).

Table 21 Dosages prescribed to all patients receiving both strong and weak opioid medicines in their first quarter 2009 when weak opioids are included and excluded from the dosage calculation (dosages not adjusted for carrying OMEQ over boundary)

Dosage within 1st quarter OMEQ/day (mg)	No. patients excluding weak opioids and tramadol	% patients excluding weak opioids and tramadol	No. patients including weak opioids and tramadol	% patients including weak opioids and tramadol	Ratio
<50	13,646	74.37	10,669	58.14	0.78
50-99	2,409	13.13	4,214	22.97	1.75
100-149	878	4.79	1,538	8.38	1.75
150-199	539	2.94	761	4.15	1.41
≥ 200	877	4.78	1,167	6.36	1.33
Total	18,349		18,349		
>120	1,812	9.875198	2,634	14.35501	1.45

5.4.2. Dosages of opioid medicine prescribed per patient

Almost three quarters (73.62%) of the patients have less than 10mg OMEQ in their first quarter in 2009 and most of these patients (57.16% of all patients) never have more than

10mg OMEQ or more in any one quarter within their follow up time. Thus, the vast majority of patients only receive low dosages of opioid whilst contributing data to the study. Only 4,508 (0.86%) patients had over 120mg OMEQ in their first quarter in 2009. By the end of the five year time period, 13,264 (2.54%) had had at least one quarter in which they had over 120mg OMEQ (Table 22).

Table 22 Dosage category of patients in first patient quarter 2009 and highest quarter in study

Dosage OMEQ/day (mg)	No. patients first quarter 2009	Percent	No. patients highest ever quarter whilst in study	Percent
<10	384,082	73.62	298,211	57.16
10-19	67,017	12.85	87,877	16.84
20-29	27,123	5.2	41,482	7.95
30-49	22,127	4.24	40,584	7.78
50-99	15,242	2.92	34,935	6.7
100-149	2,995	0.57	9,390	1.8
150-199	1,189	0.23	3,387	0.65
≥200	1,958	0.38	5,867	1.12
Total	521,733		521,733	
>120	4,508	0.86	13,264	2.54

5.4.2.1. Dosages of opioid prescribed to new and existing opioid medication users

Almost one in ten existing users of opioid medication (9.13%) received prescriptions for opioid medication totalling more than 50mg OMEQ/day in the first quarter in comparison to only 0.47% of new patients. Only a very small number of new users received prescriptions

for opioid medication over 120mg OMEQ/day in their first quarter 2009 (0.03%). In comparison, 2.02% of existing patients have over 120mg OMEQ/day (Table 23).

Table 23 Dosages prescribed to new and existing users of opioid medicines in their first quarter in 2009

Dosage OMEQ/day (mg)	Number of new opioid users first quarter 2009		Number of existing opioid users first quarter 2009	
<10	249,202	88.01	106,940	53.26
10-19	23,426	8.27	39,007	19.43
20-29	5,874	2.07	19,303	9.61
30-49	3,343	1.18	17,145	8.54
50-99	1,178	0.42	12,879	6.41
100-149	98	0.03	2,651	1.32
150-199	18	0.01	1,068	0.53
≥200	18	0.01	1,784	0.89
Total	283,157		200,777	
>120mg	78	0.03	4,062	2.02

This analysis only contains patients with a year's worth of data prior to first opioid prescription in 2009 thus the number of high dose patients within this table does not sum to the number of high dose patients in Table 22

5.4.3. Opioid regime used by patients at different dosages

In the top 3 dose bands, most patients are receiving more than one opioid medicine. For patients receiving over 120mg OMEQ/day, just over half of patients received more than one opioid medicine (52.99% of patients received more than one drug) with approximately one in eight patients receiving at least three drugs (13.04%) (Table 24).

Over 120mg OMEQ/day, only a small proportion of patients receive only weak opioids, tramadol or both weak opioids and tramadol (6.28%). However, in the 100-149mg OMEQ

category, 1 in 4 patients are receiving (24.58%) tramadol or tramadol in combination with a weak opioid. Of the patients receiving strong opioids at dosages over 120mg OMEQ/day 40.28% also received a weak opioid or tramadol (Table 25).

Over 120mg OMEQ/day patients are most likely to receive modified release opioids or a combination of modified and immediate release opioids. Just under two thirds of patients (64.02%) received modified release and immediate release opioids, with 30.57% receiving modified release opioids only (Table 26).

There were markedly different combinations of drugs within the varying dose bands. At lower dosages, weak opioids dominate and are usually used alone (i.e. the patient does not receive any other opioid drugs within a particular quarter). Strong opioids are used at low dosages with 14.05% of patients receiving strong opioids within the 20-29mg OMEQ/day band and 20.41% of patients using strong opioids within the 30-49mg OMEQ/day band. At the highest dose bands (150-199mg and ≥200mg OMEQ/day), almost all (93.86% and 99.24% of patients receive strong opioids or strong opioids in combination with weak opioids and/or tramadol (Table 25). Of the highest dose patients who use a single drug only, morphine is the most commonly used drug followed by fentanyl, oxycodone and buprenorphine. Morphine and oxycodone were more likely to be used alone, whilst fentanyl is likely to be used in combination with other drugs (Table 27).

Table 24 Number of opioid drugs prescribed to patients in their first quarter of usage in 2009, stratified by dosage prescribed

Dosage band OMEQ/day (mg)	Total number patients	Number of drugs prescribed per quarter				
		1	2	3	4	5
<10	384,082	369,001 (96.07)	14,715 (3.83)	365 (0.10)	1 (0.00)	0 (0.00)
10-19	67,017	51,809 (77.31)	13,945 (20.81)	1,226 (1.00)	36 (0.05)	1 (0.00)
20-29	27,123	19,213 (70.84)	6,852 (25.26)	957 (3.53)	98 (0.36)	3 (0.01)
30-49	22,127	14,310 (64.67)	6,724 (30.39)	968 (4.37)	114 (0.52)	11 (0.05)
50-99	15,242	9,033 (59.26)	5,134 (33.68)	906 (5.94)	154 (1.01)	15 (0.10)
100-149	2,995	1,366 (45.61)	1,265 (42.24)	322 (10.75)	35 (1.17)	7 (0.23)
150-199	1,189	559 (47.01)	476 (40.03)	130 (10.93)	22 (1.85)	2 (0.17)
≥200	1,958	907 (46.32)	791 (40.4)	221 (11.29)	35 (1.79)	4 (0.20)
Total	521,733					
>120	4,508	2,119 (47.01)	1,801 (39.95)	506 (11.22)	73 (1.62)	9 (0.2)

Table 25 Potency of opioid drugs prescribed to patients in their first quarter of usage in 2009, stratified by dosage prescribed

Dosage OMEQ / day	0-9 mg	10-19 mg	20-29 mg	30-49 mg	50-99 mg	100-149 mg	150-199 mg	≥200 mg	>120 mg
Potency									
weak	360,484 (93.86)	35,630 (53.17)	9,040 (33.33)	2,552 (11.53)	300 (1.97)	14 (0.47)	1 (0.08)	2 (0.10)	10 (0.22)
tramadol	13,862 (3.61)	16,339 (24.38)	9,228 (34.02)	10,399 (47.00)	6,537 (42.89)	342 (11.42)	39 (3.28)	13 (0.66)	142 (3.15)
weak and tramadol	5,606 (1.46)	10,470 (15.62)	5,046 (18.60)	4,661 (21.06)	2,795 (18.34)	380 (12.69)	34 (2.86)	6 (0.31)	131 (2.91)
strong	2,702 (0.70)	1,992 (2.97)	1,650 (6.08)	1,868 (8.44)	2,498 (16.39)	1,154 (38.53)	615 (51.72)	1,163 (59.40)	2,409 (53.44)
strong and weak	1,259 (0.33)	1,813 (2.71)	1,245 (4.59)	1,321 (5.97)	1,419 (9.31)	486 (16.23)	256 (21.53)	425 (21.71)	934 (20.72)
strong and tramadol	125 (0.03)	426 (0.64)	475 (1.75)	763 (3.45)	1,106 (7.26)	417 (13.92)	171 (14.38)	254 (12.97)	620 (13.75)
strong, weak and tramadol	44 (0.01)	347 (0.52)	439 (1.62)	563 (2.54)	587 (3.85)	202 (6.74)	73 (6.14)	95 (4.85)	262 (5.81)
%weak / tramadol / weak and tramadol	98.93	93.17	85.95	79.59	63.2	24.58	6.22	1.07	6.28

Table 26 Release profiles of opioid drugs prescribed to patients in their first quarter of usage in 2009, stratified by dosage prescribed

Dosage OMEQ / day	IR only	MR only	Both IR & MR
<10 mg	380,335 (99.02)	2,392 (0.62)	1,355 (0.35)
10-19 mg	60,550 (90.35)	3,358 (5.01)	3,109 (4.64)
20-29 mg	21,652 (79.83)	2,668 (9.84)	2,803 (10.33)
30-49 mg	14,872 (67.21)	3,319 (15)	3,936 (17.79)
50-99 mg	6,376 (41.83)	3,939 (25.84)	4,927 (32.33)
100-149 mg	386 (12.89)	913 (30.48)	1,696 (56.63)
150-199 mg	51 (4.29)	374 (31.46)	764 (64.26)
≥ 200 mg	70 (3.58)	560 (28.6)	1,328 (67.82)
Total	484,292 (92.82)	17,523 (3.36)	19,918 (3.82)
>120 mg	244 (5.41)	1,378 (30.57)	2,886 (64.02)

Table 27 Opioid drug types prescribed to patients in their first quarter of usage in 2009, stratified by dosage prescribed

	Dose Grouping in first quarter 2009 (OMEQ / day)							
	0-9 mg	10-19 mg	20-29 mg	30-49 mg	50-99 mg	100-149 mg	150-199 mg	≥200 mg
Total pts in dose group	384,082	67,017	27,123	22,127	15,242	2,995	1,189	1,958
	drugs used as single drug only							
codeine	274,335 (74.35)	26,803 (51.73)	6,007 (31.27)	586 (4.10)	40 (0.44)	3 (0.22)	1 (0.18)	1 (0.11)
dihydrocodeine	77,366 (20.97)	5,587 (10.78)	1,887 (9.82)	1,261 (8.81)	153 (1.69)	8 (0.59)	0 (0.00)	1 (0.11)
tramadol	13,862 (3.76)	16,339 (31.54)	9,228 (48.03)	10,399 (72.67)	6,537 (72.37)	342 (25.04)	39 (6.98)	13 (1.43)
morphine	1,001 (0.27)	563 (1.09)	519 (2.70)	616 (4.30)	883 (9.78)	425 (31.11)	192 (34.35)	422 (46.53)
buprenorphine	893 (0.24)	1,024 (1.98)	691 (3.60)	573 (4.00)	474 (5.25)	127 (9.30)	55 (9.84)	86 (9.48)
fentanyl	108 (0.03)	82 (0.16)	181 (0.94)	266 (1.86)	503 (5.57)	259 (18.96)	161 (28.80)	197 (21.72)
oxycodone	372 (0.10)	187 (0.36)	129 (0.67)	251 (1.75)	414 (4.58)	201 (14.71)	111 (19.86)	185 (20.40)
dextropropoxyphene	640 (0.17)	909 (1.75)	386 (2.01)	222 (1.55)	17 (0.19)	0 (0.00)	0 (0.00)	0 (0.00)
	proportion of drugs used alone or in combination							
codeine	287,595 (74.88)	38,891 (58.03)	11,880 (43.80)	5,978 (27.02)	3,570 (23.42)	748 (24.97)	268 (22.54)	369 (18.85)
dihydrocodeine	87,139 (22.69)	10,666 (15.92)	4,228 (15.59)	3,292 (14.88)	1,697 (11.13)	360 (12.02)	104 (8.75)	157 (8.02)
tramadol	19,637 (5.11)	27,582 (41.16)	15,188 (56.00)	16,386 (74.05)	11,025 (72.33)	1,341 (44.77)	317 (26.66)	368 (18.79)
morphine	1,583 (0.41)	1,615 (2.41)	1,339 (4.94)	1,754 (7.93)	2,308 (15.14)	940 (31.39)	434 (36.50)	913 (46.63)

Dose Grouping in first quarter 2009 (OMEQ / day)								
	0-9 mg	10-19 mg	20-29 mg	30-49 mg	50-99 mg	100-149 mg	150-199 mg	≥200 mg
buprenorphine	1,505 (0.39)	2,191 (3.27)	1,727 (6.37)	1,735 (7.84)	1,679 (11.02)	466 (15.56)	190 (15.98)	234 (11.95)
fentanyl	169 (0.04)	287 (0.43)	449 (1.66)	671 (3.03)	1,249 (8.19)	752 (25.11)	455 (38.27)	806 (41.16)
oxycodone	505 (0.13)	511 (0.76)	627 (2.83)	627 (2.83)	891 (5.85)	369 (12.32)	214 (18.00)	418 (21.35)
dextropropoxyphene	785 (0.20)	1,139 (1.70)	519 (1.91)	361 (1.63)	103 (0.68)	18 (0.60)	5 (0.42)	14 (0.72)
Proportion of drugs used as single drug only								
codeine	0.95	0.69	0.51	0.10	0.01	0.00	0.00	0.00
dihydrocodeine	0.89	0.52	0.45	0.38	0.09	0.02	0.00	0.01
tramadol	0.71	0.59	0.61	0.63	0.59	0.26	0.12	0.04
morphine	0.63	0.35	0.39	0.35	0.38	0.45	0.44	0.46
buprenorphine	0.59	0.47	0.40	0.33	0.28	0.27	0.29	0.37
fentanyl	0.64	0.29	0.40	0.40	0.40	0.34	0.35	0.24
oxycodone	0.74	0.37	0.21	0.40	0.46	0.54	0.52	0.44
dextropropoxyphene	0.82	0.80	0.74	0.61	0.17	0.00	0.00	0.00

5.4.4. Probability of continuing to receive opioid medicines for the next five years based on dosage in first quarter 2009 and length of time on opioids

Patients using small dosages (less than 10mg OMEQ/day) of opioid medication for short periods of time are likely to stop taking this medication, at least in the short term. Only 8.5% continue using opioids for the next five years without a 90 day gap if they have been using opioids for less than six months. There seems to be a change in pattern around one and half years of prior use in which the probability of continuation declines at a slower rate. Patients using small dosages of opioid medication that have been receiving prescriptions for longer periods are more likely to continue opioid medication. Even if patients have been using opioid medication for over ten years, there is a 45.5% chance they will stop using medication over the next five years (Table 28).

Where people have been using over 50mg OMEQ/day per quarter for over a year, they are more likely to continue this usage over the next five years than those receiving prescriptions for a lower dosage. Approximately 60-70% of patients in this group continue to use opioid medication for the next five years (Table 28). There is a large overlap in the dosage band results for the groups above 10mg OMEQ/day, particularly after the first 2 years (Figure 10). However, there is still an upward trend towards increasing dose as can be seen by plotting the results from 0-9mg, 10-19mg and 50-99mg OMEQ/day as separate groups (Figure 11).

Table 28 Probability of continuation in prescribing of opioid medicines for next five years, stratified by dosage prescribed to the patient in their first quarter in 2009 and length of continuous use before 2009

	Probability of continuous opioid use for next five years (no. pts at risk at 5 years)					
	Oral morphine equivalents received in the first quarter of 2009					
Years of continuous use before 2009	<10	10-19	20-29	30-49	50-99	>120
0-0.5	0.085 (1480)	0.173 (703)	0.218 (341)	0.289 (340)	0.349 (189)	0.356 (29)
0.5-1	0.178 (1518)	0.311 (855)	0.302 (362)	0.39 (395)	0.454 (252)	0.520 (53)
1-2	0.276 (2551)	0.427 (1661)	0.439 (860)	0.504 (870)	0.581 (705)	0.624 (187)
2-3	0.358 (1927)	0.506 (1408)	0.535 (762)	0.539 (747)	0.639 (686)	0.676 (219)
3-4	0.412 (1435)	0.574 (1181)	0.596 (634)	0.618 (727)	0.678 (579)	0.663 (193)
4-5	0.449 (1099)	0.574 (907)	0.634 (544)	0.613 (537)	0.702 (527)	0.699 (192)
5-6	0.474 (924)	0.614 (869)	0.607 (419)	0.648 (437)	0.723 (458)	0.738 (182)
6-7	0.491 (748)	0.657 (707)	0.638 (393)	0.639 (402)	0.704 (383)	0.757 (150)
7-8	0.499 (650)	0.608 (600)	0.691 (404)	0.663 (372)	0.719 (360)	0.79 (151)
8-9	0.513 (547)	0.646 (486)	0.665 (303)	0.684 (282)	0.726 (321)	0.737 (106)
9-10	0.523 (466)	0.645 (449)	0.729 (333)	0.649 (262)	0.747 (276)	0.768 (114)
10-20	0.545 (1692)	0.666 (1616)	0.691 (1105)	0.701 (996)	0.741 (985)	0.73 (354)

Figure 10 Probability of existing users of opioid medicines continuing to receive prescriptions for opioid medicines for next five years, stratified by dosage prescribed to the patient in their first quarter in 2009 and length of continuous use before 2009 (including 95% confidence interval)

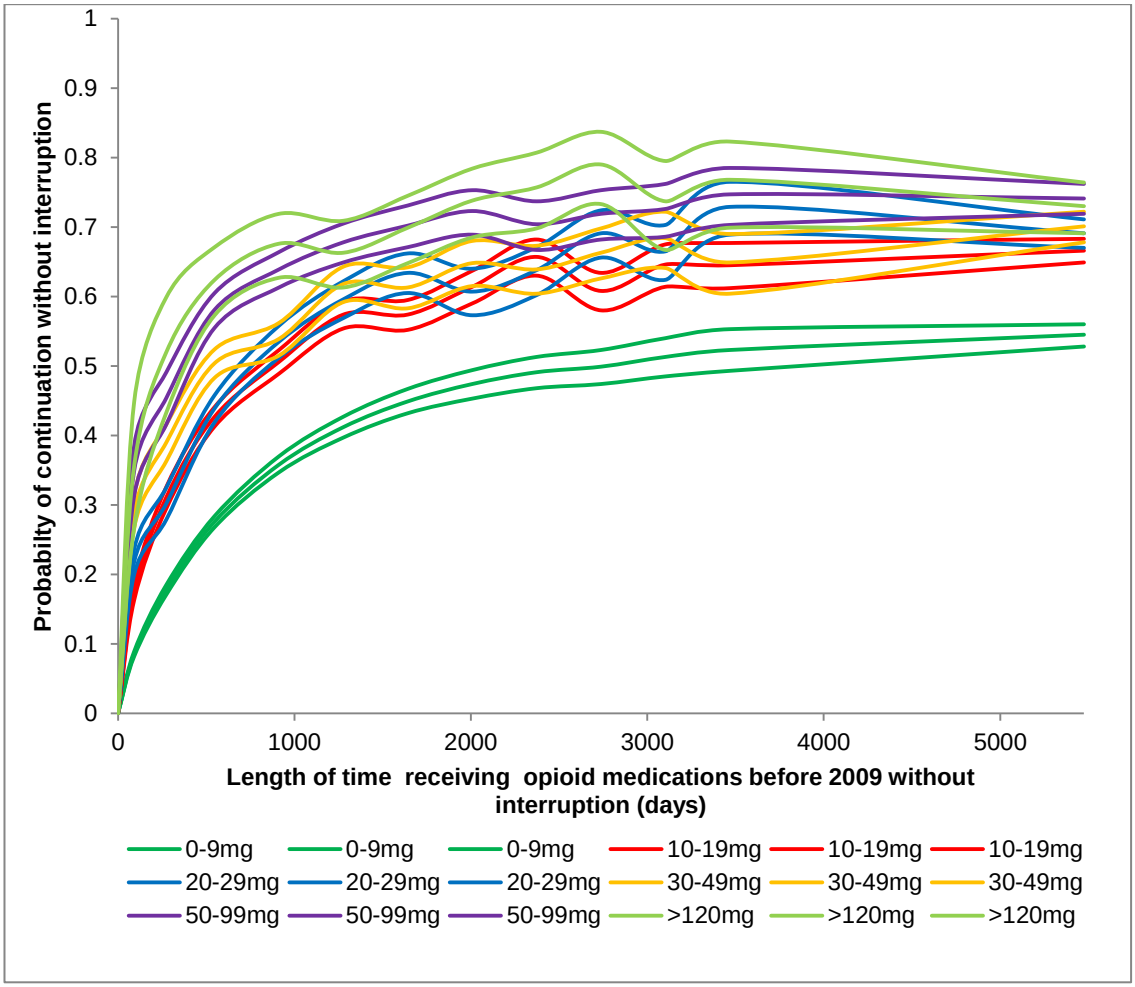
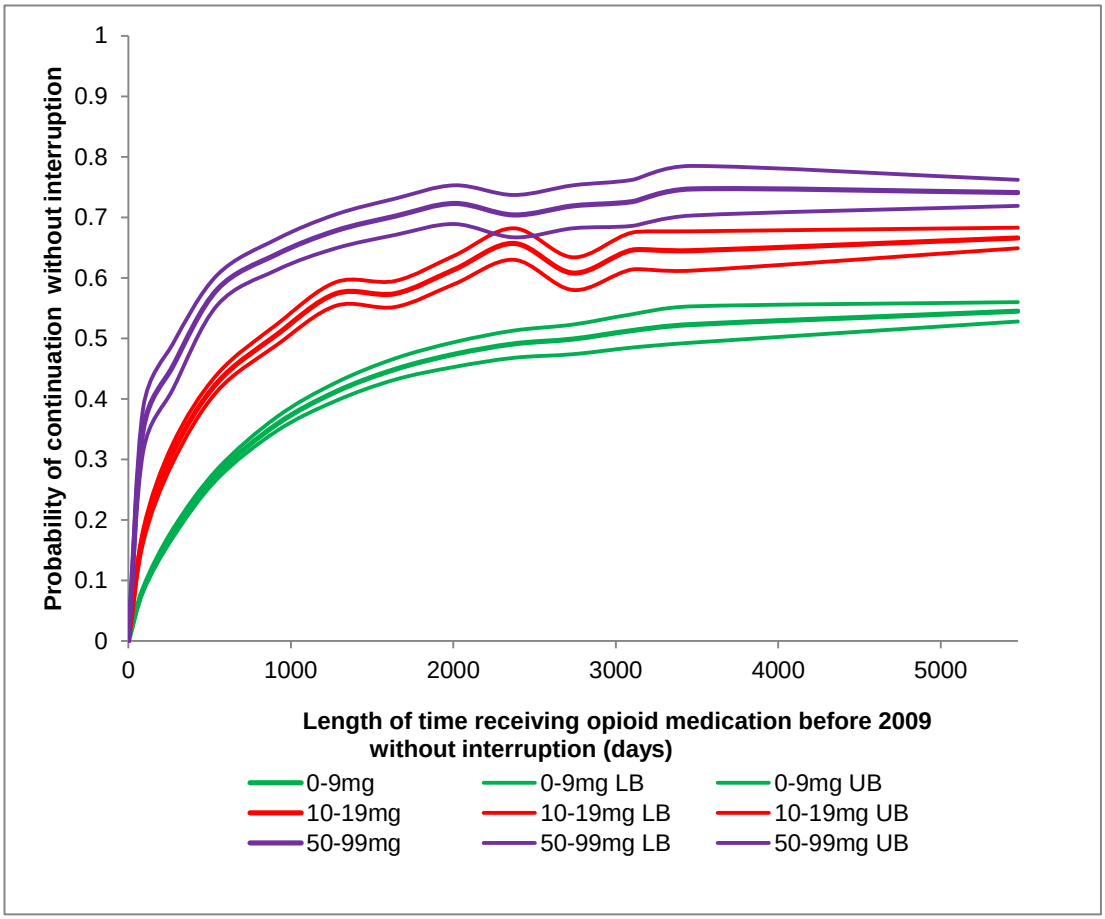


Figure 11 Probability of existing users of opioid medicines continuing to receive prescriptions for opioid medicines for next five years, stratified by dosage prescribed to the patient in their first quarter in 2009 and length of continuous use before 2009 (including 95% confidence interval), for selected dosage groups only

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5.5. Discussion

5.5.1. Dosages received by patients

Including the OMEQ from the weak opioids and tramadol increased the number of patients who have a quarter over 120mg OMEQ/day by a factor of 1.45 over strong opioids alone. This means that weak opioids and/or tramadol do contribute a significant proportion of the dosage and should be included in future studies that require the calculation of total opioid dose.

When all the non-cancer patients were included in an analysis, out of the 521,733 non-cancer patients in the study cohort, 4,508 patients (0.86%) receive prescriptions for amount of opioid totalling greater than 120mg OMEQ/day in the first quarter of the study (first quarter 2009). This seems a small proportion, however, as so many patients start opioid medicines, (10.58% of the population in one year), this will actually be a large number of patients in practice over the course of a year.

Over the next five year period of the study, 13,264 patients (2.54%) who received opioids in 2009 (including new and existing patients) went on to receive greater than 120mg OMEQ/day in the next five year period. However, this does not account for the fact that some patients will die or transfer surgeries. If they do this, then the length of follow up will be shortened. In another study in the U.K., it was found that patients that have shorter follow up times are more likely to have lower dosages [205]. However, this still shows that over time some patients who were not receiving high dosages before will receive higher dosages. This means that opioid use must change over time, for some patients at least.

Just under one in ten existing opioid medicine users (9.15%) are receiving dosages of over 50mg OMEQ/day. This dosage has been linked to an increased risk of overdose (Section 2.11.4) in studies in other countries. The National Canadian guidelines [99] now recommend restriction of the daily dose to 50mg OMEQ/day, though the guideline group acknowledge that many patients will be willing to accept the risks associated with a dose higher than this.

This means that prescribers must be able to evaluate the benefits of opioid use in patients using opioids and this is documented in the patient record, for example, the Opioids Aware guidelines recommend patients keep a diary, document the medicines that they take and record measurable outcomes of enjoyment of life [69].

The only other U.K. studies that report dosage include only new opioid users or patients receiving strong opioids (excluding tramadol). A study that also used CPRD data, that looked at all opioids but excluded buprenorphine [199], Chevalier et al, reported the mean dosage used by patients who were started on weak and strong opioids split into groups according to the subsequent length of usage. The study also used CPRD data for patients starting opioid medicines between November 2006 and October 2011. In the weak group (which included tramadol) of acute opioid users (less than 30 days) the mean was 26.3mg OMEQ/day, for subacute weak opioid users (>30 but less than 182 days) 29.6mg OMEQ/day and in chronic users of opioids (greater than 182 days) was 36.1mg OMEQ/day. This appears much higher than in the current study, (as the vast majority of patients receive lower dosages) however the numbers of patients appear lower in the Chevalier study (even accounting for the 40% decrease for HES linkage) indicating that potentially not all opioid prescriptions are included. If the weaker opioid combinations were excluded from this study this would explain the higher dosages at index. This study also used the daily dose to assess dosage. This is likely to give higher dosages as this represents the prescribers intended dose which is likely to be higher than the calculated dose. However, the fact the method used in this chapter will underestimate dosages in patients that only receive 30 days treatment, is a major limitation of this study (see limitations section).

5.5.2. Opioid regime used by patients at different dosages

Over half (52.99%) of patients receiving the highest dosages (>120mg OMEQ/day) were using multiple opioids, with 40.28% received weak opioids and tramadol in addition to a strong opioid. Most patients receiving the highest dosages are receiving modified release medications with almost two thirds receiving immediate release and modified release.

Fentanyl and morphine were the drugs most commonly prescribed at higher dosages and fentanyl was more likely to be used in combination with another opioid. Therefore, a number of patients receiving the highest dosages are using combinations of opioids either in the form of multiple opioid drugs or multiple release profile types.

The fact that strong and weak opioid drugs are used across a range of dosages means that excluding certain types of opioid means that some patients using equivalent OMEQ dosages will not be included in a study. Within the groups some patients are prescribed tramadol and are receiving higher dosages than those taking morphine. However, for the highest dosage groups most patients will receive some strong opioid analgesics. So, if future studies only intended to include patients on the very highest dosages or prescribers identify patients with very high dosages almost all of these patients will be using strong opioids alone or in combination with weak opioids or tramadol.

Although use of dosages of over 120mg OMEQ/day appears unlikely when looking at all opioid patients, this is likely to vary depending on the drug the patient receives and the dosage range for the drug. Patients that are only taking codeine, by far the vast majority of patients, are not likely to receive high dosages unless they are allowed to order more prescriptions than the prescribed dose. This was unlikely at very high dosages however, worthy of note, 300 patients had received prescriptions for at least twice the maximum dosage of codeine meaning that at some surgeries it may be possible to order more medication than should be required, this may warrant further investigation.

Increasing dose is linked to increasing number of drug types. This may be because patients who consume high dosages are using more than one opioid to treat their pain, alternatively, this may be as a result of the method of measuring the opioid prescribing patterns. The prescriber may have issued multiple prescriptions in the 91 day period and intended for the patient to switch drugs rather than take them at the same time in an attempt to find that drug that shows benefit with minimal side effects. Nevertheless, if the prescriptions were dispensed the patient would have a particular dosage of drug available which they could

potentially consume. Given the large number of patients using multiple drugs this is unlikely to explain all the results. Further studies, that involve looking at dispensing of prescriptions and asking patients what they actually have consumed and comparing this to their opioid prescribing patterns would enable a more accurate estimation of dosage consumed in future database studies. An evaluation of how patients determine the need for using additional medications and the benefits associated with additional medication is also needed. This may also be a useful study to conduct as, if patients are not taking all the medication available to them then this medication may be open to diversion, a problem that is common in the U.S.A. [209].

At high dosages the vast majority (two thirds) of patients receive modified release and immediate release preparations. This practice is advocated in the current U.K. guidelines. However, the use of modified release opioids has been called into question because of the lack of evidence associated with their use, in that they have not been found in clinical trials to provide better pain relief to immediate release opioids [210]. In one survey (which included data on dosages consumed from pharmacy records in conjunction with self-reported problems and concerns), of 1,781 privately insured patients in the U.S.A., patients receiving time dependent opioids were found to receive higher dosages of opioid medication, 97.2mg OMEQ/day in the time dependent category versus 37.2mg OMEQ/day in the pain-contingent group. Patients in the time dependent category were more likely to worry about dependence and have family and friends that worry about their dependence. They were also more likely to complain that they could not think clearly. However, as the authors note, it is likely that certain types of patients are more likely to be prescribed time dependent opioids, for example patients who have characteristics that mean they are more likely to become addicted may be more likely to be prescribed time dependent opioids [211]. As combinations are such a common practice in the U.K., further work is urgently required to determine whether patients are obtaining worthwhile benefits using these regimes (in terms of pain relief, function and quality of life) and in what circumstances patients use these regimes and whether they have adequate training in how to manage these medications.

5.5.3. Persistence with medication by dosage and length of time receiving opioids

If the persistence to opioid medication is measured in all medicine users it appears that only a very small proportion of new opioid medicine users (2.06%, Section 4.4.2) and a larger proportion of existing users (34.82%, Section 4.4.3) continuously receive opioid medication for five years. However, it can be seen from the analysis of persistence in existing patients that the probability of continuing to receive prescriptions for opioid medication in the long term is linked to the length of time patients have been receiving opioid medication and the dosage (or potentially the drug) that they are receiving.

As seen in the previous chapters the probability of continuing to receive opioid medication increases the longer the patient has been continuously receiving opioid prescriptions for. This can be seen at all dosages. In the dosage categories of 10mg OMEQ/day and over, in patients that have been receiving prescriptions for two years, over half of patients will continue to receive opioid prescriptions for the next five years at least, on top of the two years they have already been receiving medication.

Patients receiving higher dosages of opioid medication were more likely to continue opioid use over the next five year period. The higher the dose the more likely patients were to continuously receive opioid prescriptions without a gap. Two thirds of patients (63.9%) that have been receiving dosages of 50-99mg OMEQ/day, and have been taking for two-three years will continue to receive opioid medication for the next five years. This result could act as a talking point for patients and prescribers when considering chronic pain plans for the future.

A previous small study of patients using electronic medical records in one U.K. primary care surgery [124], which looked at the proportion of opioid patients that received medication reviews, found that the likelihood of a review was related to the age of the patient (potentially due to the number of medications triggering on screen reminders), with older patients receiving reviews rather than patients with risk factors such as dose, concurrent use of benzodiazepines, mental health diagnosis. The study recommended that there is a need for

a “more structured and specific” medication review system. The study also found that the details of the medication review were not recorded and so it was difficult to assess what the prescriber had undertaken as part of the review. Larger scale studies, in multiple surgeries may be required to confirm these findings to see how many patients have outcomes documented in their notes and how many patients cease opioid medication as a result of these reviews. Patients that are taking dosages that may indicate they are more likely to continue opioid medicines in the long-term could be targeted for reviews.

5.5.4. Strengths and limitations

In comparison to previous studies from the U.K., that measure dosage this study included all opioids that patients were prescribed within a 91 day time period, previous studies have only included strong opioids or extended release opioids. The probability of persistence was calculated and stratified by previous use and dosage, this provides further insight into the probability that patients continue to receive opioid medicines.

However, this study has a number of limitations. There was a requirement for patients to have at least one full quarter of data which excluded a number of patients that received high dosages within this quarter. However, due to the fact that these patients contribute for less than one quarter they are unlikely to be receiving opioids in the long-term. As the dosage is calculated over a period of 91 days then patients who use higher dosages for short periods may have their dosage underestimated as the dosage is calculated as an average over the whole time period. This also means that only patients who receive higher dosages for at least 3 months are recorded as receiving high dosages. Thus identifying only the most serious high dose patients and not identifying short term high dose patients.

The length of time a patient is likely to continue opioid medication can be predicted based on the length of time using opioid medication and the dosages used however this also is likely to depend on the drug used and the numbers of drugs used before the patient received the particular drug they were taking at the time of the study. It is possible that the patients that are more likely to continue within a dose band are the patients on higher dosages of a

particular drug so it is potentially a combination of the drug type used and the dosage that would make the most accurate predictor of the likelihood of continuation of opioid medication. A further study could examine whether patients on different drugs at similar dosages were more likely to continue use when specific drugs were used. However, this would lead to a more complex prediction tool.

In the next chapter the probability of receiving a high dose at some point in the study will be calculated. Patients may also decrease dosage again, to address this problem the time to low dose or discontinuation of opioids will be calculated for patients receiving high dosages of opioid.

5.5.5. Summary

In this chapter the dosage that patients were receiving was calculated from their total amount of opioid prescribed in their first 91 day period in 2009. Within this first quarter, only 0.86% of patients received a prescription for over 120mg OMEQ/day. However if we follow the patients for five years 2.54% of patients will have a quarter in which they receive a high dose.

The analysis within this chapter also looked at the drugs used a different dosage bands. A large proportion of patients were receiving multiple opioids at higher dosages. The study in this chapter also identified that patients taking higher dosages are more likely to continue to be prescribed opioid medicines continuously for longer periods.

In this chapter the dosage calculated and tabulated was the dosage in only one quarter. In the next chapter the time to high dosage will be calculated and the characteristics of patients who receive high dose opioid medication will be analyses in addition to the characteristics of patients that receive high dosages of opioid for long periods.

Chapter 6. Characteristics associated with the probability of receiving high dose and long-term high dose opioid medicine

6.1. Introduction

In Chapter 5, a method was developed to measure the dosages of opioid medicines prescribed to patients. When this method was used to determine dosages within the cohort, a small but significant proportion of patients received high dosages (over 120mg OMEQ/day) for at least 91 days. Previous studies have found an association between high dose use and adverse selection, indicated by the presence of certain patient characteristics (Section 2.9.2); a key characteristic being a diagnosis of a psychological disorder, for example, depression. However, these studies have been carried out in countries other than the U.K and opioid prescribing is subject to many influences which vary from country to country [14]. In the U.K., it is possible that high dose usage is not associated with psychological disorders if prescribers are better at identifying these disorders, (do not increase dosages in response to pain intensity increases driven by distress) and the appropriate systems are in place to manage depression when it occurs with chronic pain. However, this may not be the case for reasons outlined in the literature review (Section 2.10). If it is the case, that psychological factors are linked to high dosages, then future research and policy changes could address whether prescribing is appropriate in these situations.

The relationship between patient characteristics and the probability of a patient being prescribed a strong opioid (including the probability of stepping up and down to and from a strong opioid) has previously been studied in the U.K., but not how these patient factors affect how dosages increase [27, 28]. Although patients who take strong opioid medications have a greater possibility of receiving high dose opioid medication due to the fact there are no maximum dosages of strong opioids, they can also continue to take only low dosages of opioid medication [205]. Indeed, the results from Chapter 5 show that only a small proportion of patients that receive strong opioid medication (especially if this includes tramadol) receive a high dose of opioid medication. However, the analysis in chapter 5 does not take into account the length of time a patient has been prescribed opioid medicine and the dosage actually consumed by the patient may be underestimated, as the amount prescribed is calculated over a 91 day period.

The analyses in this chapter look at the characteristics (demographic, physical and psychological comorbidities) that affect high dose prescribing of opioids using two approaches. The first (Study 1), aimed to explore what characteristics are associated with patients ever being prescribed high dosages of opioid medicines (total sum >120mg OMEQ per day) and the second (Study 2), to see what characteristics are associated with patients continuing to be prescribed high dosages of opioid medicines. These two approaches are necessary as comparing just the characteristics of high and low dose patients does not tell us whether an association is due to an increased probability of starting high dose or an increased probability of continued high dose use. This is important as how the characteristic affects whether a patient is prescribed high dose or continues at a high dose is likely to affect how future interventions are tailored towards specific characteristics i.e. focus on preventing high dose use or stopping it once it starts.

In Study 1, patients who only received opioids in the first quarter of opioid medicine use in the first episode of opioid medicine use were excluded from analysis. This is because there are many patients who use opioids for a very short term period (Section 4.4.2), which could be because they are patients suffering from acute pain or discontinue quickly because they experience adverse events. For comparing to high dose use, we are interested only in chronic pain patients as we are not interested in comparisons of acute and high dose opioid medicine users. Only patients who received opioids in at least two consecutive quarters were included in the control group and high dose group.

Also in this chapter (in study 2), characteristics of patients who receive high dose opioid medicines are presented. This is to provide an overview of the types of patients prescribed high dose medicines rather than just the characteristics of new high dose opioid users. The characteristics are presented in terms of age and whether they are new or existing users. This is because previous studies [110] have identified that younger patients are more likely to have psychological comorbidities than older patients and this analysis will show whether this is the case in the U.K. Also, the characteristics of new and existing users associated with high dose use are also presented, because the new users of opioid medicines have only

started opioid use relatively recently (whereas existing users have been potentially taking them for years).

6.2. Aims and Objectives

The aim of this chapter is to describe the factors associated with high dose and long-term high dose use in the U.K.

- To identify what factors predict high dose opioid use in new opioid medicine users
- To describe the characteristics of patients who receive high dose medication in new and existing opioid users (who have not received high dose before)
- To identify the factors associated with long-term opioid use once high dose opioid use has started

6.3. Method

A flow chart of the cohort selection and analyses for Chapters 5 and 6 can be found in Appendix 1.

6.3.1. Study design and cohort selection

This chapter includes two retrospective longitudinal cohort studies conducted on two subgroups of patients from the cohort who received an opioid prescription in 2009 (Section 3.3.2).

6.3.1.1. Study one cohort selection

For the first study, patients newly starting opioid medication in 2009 with one year of data before their first prescription in 2009 (excluding patients with less than one quarter of data, Section 5.3.1 definition) were followed from their first prescription in 2009 until end of episode of opioid medicine (defined as a patient having a quarter in which a patient was prescribed no opioid medicines), death, leaving their surgery or end of upload of data to CPRD. Patients were only included if they had prescriptions in at least their first and second consecutive quarters after first prescription in 2009.

Patients were excluded from analysis if they did not have one year's worth of up to standard registration before first prescription in 2009 or if they did not have linkage to data on socioeconomic status.

6.3.1.2. Study two cohort selection

For the second study, both new and existing (in 2009) opioid medicine users who were calculated to have been prescribed high dose opioid medication (>120mg OMEQ/ day using method described in Section 5.3.3) in a quarter after 2009 but who did not start on a high dose medication in their first quarter in 2009 or were prescribed high dose opioid medication in any quarter in the two years prior to 2009, were followed until their data was censored, they discontinued high dose or they died. Patients were free to start high dose at any point

after 2009 so the follow up time after first high dose quarter varied depending upon when the patient had a high dose quarter.

Patients were excluded from analysis if they did not have one year's worth of up to standard registration before first prescription in 2009 or if they did not have linkage to data on socioeconomic status.

6.3.2. Opioid utilization measures - Study One and Study Two

6.3.2.1. Definition of a patient who is prescribed high dose opioid medicine

The dosage (OMEQ/day) for all whole quarters of opioid medicine use after 2009 was calculated for each patient (Section 5.3.3). High dose use was defined as a dosage of greater than 120mg OMEQ/day as per the "Opioids Aware" guidelines as the dose at which the risk of harm substantially increases [69].

6.3.3. Opioid utilization measures - Study One only

In Study One, only patients who had a high dose quarter in their first episode of use were counted as patients receiving high dose opioid medication. This was because it is hypothesized that the predictors that were measured at the start of treatment would be related to a particular course of opioid medicines; if a patient had a gap then they could be receiving the medicine for a different purpose that did not relate to the first episode.

6.3.4. Opioid utilisation measures – Study Two only

6.3.4.1. Number of opioids received by patients since starting treatment

The number of different opioid medicine drug types that each patient had received since the start of their treatment was counted for each patient who had a high dose quarter. For new users of opioid medication in 2009, this was the number of opioids since 2009; for existing users of opioid medication, this was since their first prescription after a gap of 90 days between prescriptions (the start of the first "run" as defined in Section 3.3.4.11). Patients

may have been prescribed these opioid medicine drug types at the same time or at a different time in their opioid use.

6.3.4.2. Length of high dose use

In all patients (including new and existing opioid users) who received a high dose for the first time after 2009, the time to greater than one gap in high dose quarters was calculated. The quarter in which the patient received high dose before two quarters without high dose was deemed to be the last quarter the patient received a high dose. Patients were followed until they stopped high dose use due to having two consecutive quarters in which the patient was not prescribed a high dosage, discontinuation of opioids, death, or data being censored (patient switches surgeries or final upload of data to CPRD database).

6.3.5. Potential characteristics predicting high dose or long-term high dose use

Potential predictors (see below and Figure 3) were measured in Study 1 at the time of first prescription in 2009 and in Study 2 (which contained both new and existing users of opioid medication) on the date of the start of the first high dose quarter (Figure 12). This was to be able to use the characteristics of opioid medication users at the time of first prescribing or first high dose to predict outcomes based on the characteristics at that point.

6.3.5.1. Age

In Study 1, age was calculated as the age in 2009. In Study 2, age was calculated during the year in which the patient received the first high dose quarter.

6.3.5.2. Gender

Gender was as recorded in the CPRD data.

6.3.5.3. Physical comorbidities

Read Codes lists for physical comorbidities were taken from the Quality and Outcomes Framework as described in the (Section 3.3.4.8). The physical comorbidities in the first study

were measured before the first opioid prescription in 2009. In the second study, the characteristics were counted before the date at the start of the first high dose quarter.

6.3.5.4. Psychological factors

6.3.5.4.1. Antidepressant prescribing

In the first study, the presence of an antidepressant (not including prescriptions for tricyclic antidepressants (TCA) or duloxetine) in the year before and in the year after first opioid prescription in 2009 was recorded (Section 3.3.4.9). Antidepressant use was split into before and after opioid use started to establish whether the patient had psychological comorbidities before opioid use started, to attempt to distinguish between whether the patient was predisposed to high dose use before starting opioid treatment. In the second study, the presence of an antidepressant (not TCA or duloxetine prodcode list in Appendix 5) was recorded in the year before and after the start date of the first quarter of high dose use.

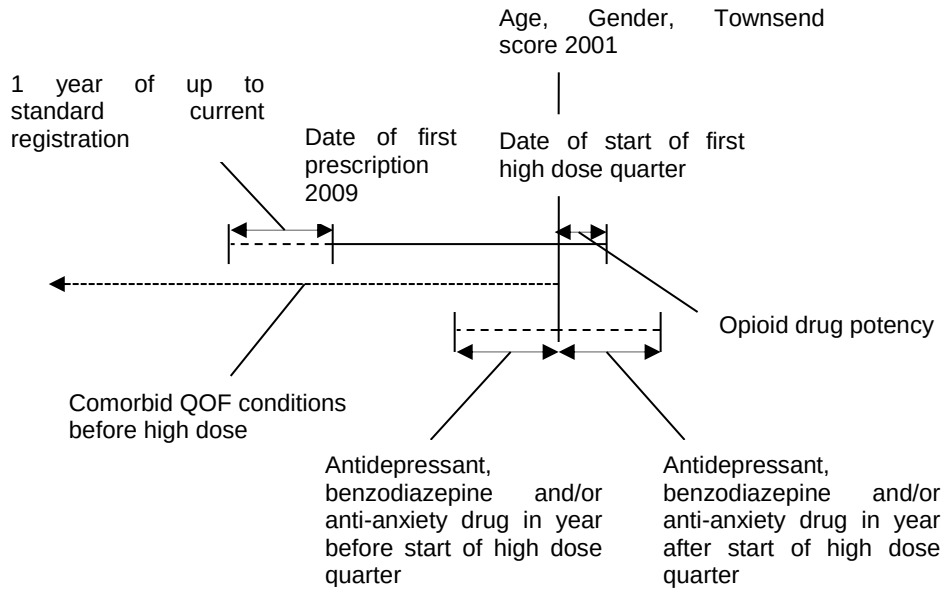
6.3.5.4.2. Read Code for anxiety or depression

The number of patients who had ever been coded with depression or anxiety diagnoses or symptoms was also included. This provided an impression of the likely psychological history of the opioid medication users and because patients may not be treated with an antidepressant for some reason. For example, the patient had tried antidepressants and found they do not work or has developed unacceptable adverse effects that mean they are unable to continue taking the medication.

6.3.5.5. Benzodiazepine and/or anti-anxiety drug prescribing

In the first study, whether a patient received a benzodiazepine and/or anti-anxiety drug in the year before or after first opioid prescription in 2009 use was recorded (Section 3.3.4.10). In the second study, benzodiazepine and/or anti-anxiety drug use was measured in the year before or after the start date of the first high dose opioid quarter (prodcode list in Appendix 6).

Figure 12 Diagram of the method of measuring patient characteristics for Study 2



6.3.5.6. Deprivation score

The quintile of Townsend deprivation score 2001 for the patient's postcode area as allocated by CPRD was used as a measure of deprivation. This variable was included, as in other studies, deprivation was found to be associated with an increased probability of receiving a strong opioid [27, 28].

6.3.5.7. Potency of drug

In the second study only, the potency of opioid used (e.g. (a) weak and or tramadol, (b) strong only or (c) both weak and strong or tramadol and strong or all three drugs) in the first high dose quarter was used as a predictor. This was included because those patients receiving prescriptions for weak opioid and or tramadol are likely to be near the maximum dose of a particular drug and so may be different to strong opioid users. The potency of each opioid drug type is defined in (Section 3.3.4.7).

6.3.5.8. Time to high dose from start of opioid treatment

In the second study, the time to high dose was measured as the time between starting opioid medication and the start of the first high dose quarter. In the case of existing users of opioid medication, the start of a "run" (Section 3.3.4.11) was used as the start date for opioid

medicine use. This was used as some patients may increase their use of opioids quickly and these patients may have different characteristics to those increasing at a slower rate which may have an effect on whether they are likely to continue high dose medication.

6.3.6. Data analysis

6.3.6.1. Study One – Odds of high dose

The characteristics (potential predictors) of patients who had a high dose quarter (and at least two quarters in which they received an opioid medicine) were compared to all other patients with greater than one quarter via calculation of odds ratios for patients who newly started opioid medication in 2009. The dependent variable was whether a patient received a quarter of high or low dose opioid medicine in the first episode of use. The independent variables were age, gender, number of comorbidities at the start of opioid medicine treatment, prescription of antidepressant in year before and after first opioid medicine treatment, prescription of benzodiazepine and/or anti-anxiety drug in the year before and after first opioid medicine treatment and deprivation score.

The effect of all factors described in the previous section on calculated odds ratios were measured using descriptive statistics and a multiple logistic regression model (univariate and adjusted). Odds ratios were reported with 95% confidence intervals. Odds ratios of greater than one were associated with a greater probability of high dose use associated with a particular variable.

6.3.6.2. Study Two - Characteristics of patients receiving high dose and time to discontinuation of high dose

Descriptive statistics were used to describe the new and existing opioid medicine users who had started high dose medication during the study period (Section 6.3.1.2).

For psychological characteristics descriptive statistics were divided into age groups to show the differences between age groups as previous studies have shown that younger patients may be more likely to have psychological comorbidities [110].

The probability of discontinuation of high dose medication was calculated using death as a competing risk (Section 4.3.3).To understand the relationship between patient characteristics and the probability patients continued to receive high dose opioid medication, hazard ratios explaining the effect of factors on rate of discontinuation of high dose opioid medication were calculated using Cox regression. Patients were followed from the time of first high dose quarter until they discontinued high dose, were censored (left the database i.e. changed surgeries or the end of data contribution by the surgery). The proportional hazards assumption was checked by reviewing Schoenfeld residuals and testing the significance of time-varying covariates (varying linearly with time) for each of the independent variables within the multivariate model. The independent variables were age group, gender, opioid drug potency in the first high dose quarter, number of comorbidities before first high dose quarter, prescribing of an antidepressant in the year before or after the start of the first high dose quarter, prescribing of a benzodiazepine and/or anti-anxiety drug in the year before or after the start of the first high dose quarter and Townsend deprivation score. Where time-varying covariates were significant, they were included as time-varying covariates in the final model.

6.4. Results

6.4.1. Study One - Characteristics affecting the odds of high dose opioid use

In the new user patient group (n=283,157), 1,386 (0.49%) patients had a quarter in which the prescriptions they were prescribed totalled over 120mg OMEQ/day at any point in their follow up. Of these patients, 739 (53.32%) patients who had greater than one quarter received a high dose in their first episode of opioid use. Of these patients, 449 patients had data linked to deprivation statistics.

6.4.1.1. Unadjusted analysis

Patient characteristics that were found to be linked to a reduced probability of high dose use in univariate analysis included age, with older patients less likely to be prescribed high opioid doses than younger patients (patients aged ≥65 years had an unadjusted odds ratio (uOR) of receiving higher dosages of 0.58 (95% CI 0.47-0.72) compared to patients aged 18-49 years. Other patient characteristics found to be associated with increased risk of receiving high dose were (1) whether a patient received an antidepressant in year before or year after they started any opioid medication, before uOR 2.20 (95% CI 1.79 - 2.72), after uOR 2.22 (95% CI 1.59 - 3.09), (2) whether a patient received any benzodiazepine and/or anti-anxiety drug in the year before or after opioid medication began, before uOR 2.60 (95% CI 2.06 - 3.27) or after uOR 3.62 (95% CI 2.81 - 4.66)) (Table 29).

6.4.1.2. Adjusted analysis

After adjustment for other characteristics, the same characteristics remained significant. In addition, an increased probability of high dose use in patients who had greater than three comorbidities before opioid use started was found. The magnitude of the effect of age remained almost identical to the univariate analysis. However, the effect of antidepressant and benzodiazepine and/or anti-anxiety drug use in the year before and after the start of opioid treatment was slightly attenuated (antidepressant use before aOR 1.81 (95% CI 1.45-2.25) antidepressant use after aOR 1.74 (95% CI 1.25-2.44), benzodiazepine and/or anti-

anxiety drug use before aOR 2.22 (95% CI 1.75-2.81) benzodiazepine and/or anti-anxiety drug use after aOR 3.17 (95% CI 2.45-4.10)). In the adjusted analysis, whether a patient had greater than three physical comorbidities was also shown to influence the risk of high dose use with aOR of 1.68 (95% CI 1.23 - 2.31) (Table 29).

Table 29. Patient characteristics associated with prescribing of high doses of opioid medicines (including new users of opioid medicines that are prescribed opioid medicines for greater than one quarter)

	Low dose (n=38,902) (%)	**High dose (n=449) (%)**	**uOR (95% CI)**	**aOR (95% CI)**
Age group (years)				
18-49	11,774 (30.27)	191 (42.54)	1	1
50-64	11,101 (28.54)	108 (24.05)	**0.60 (0.47 - 0.76)**	**0.62 (0.48 - 0.79)**
65+	16,027 (41.2)	150 (33.41)	**0.58 (0.47 - 0.72)**	**0.58 (0.44 - 0.75)**
Gender				
Male	15,008 (38.58)	180 (40.09)	1	1
Female	23,894 (61.42)	269 (59.91)	0.94 (0.78 - 1.13)	0.84 (0.69 - 1.02)
Number of comorbidities before start of opioid				
0	15,296 (39.32)	177 (39.42)	1	1
1	11,399 (29.3)	131 (29.18)	0.99 (0.79 - 1.25)	1.15 (0.91 - 1.45)
2	6,537 (16.8)	65 (14.48)	0.86 (0.65 - 1.14)	1.16 (0.85 - 1.58)
3 or more	5,670 (14.58)	76 (16.93)	1.16 (0.88 - 1.52)	**1.68 (1.23 - 2.31)**
Antidepressant at start of opioid (not TCA dulox)				
None	30,237 (77.73)	275 (61.25)	1	1
Before	6,635 (17.06)	133 (29.62)	**2.20 (1.79 - 2.72)**	**1.81 (1.45 - 2.25)**
Year after	2,030 (5.22)	41 (9.13)	**2.22 (1.59 - 3.09)**	**1.74 (1.25 - 2.44)**

	Low dose (n=38,902) (%)	High dose (n=449) (%)	uOR (95% CI)	aOR (95% CI)
Benzodiazepine and/or anti-anxiety drug use at start of opioid				
None	31,630 (81.31)	267 (59.47)	1	1
Before	4,653 (11.96)	102 (22.72)	**2.60 (2.06 - 3.27)**	**2.22 (1.75 - 2.81)**
Year after	2,619 (6.73)	80 (17.82)	**3.62 (2.81 - 4.66)**	**3.17 (2.45 - 4.10)**
Townsend deprivation quintile 2001				
1	7,270 (18.69)	92 (20.49)	1	1
2	7,949 (20.43)	93 (20.71)	0.92 (0.69 - 1.24)	0.91 (0.68 - 1.22)
3	8,312 (21.37)	87 (19.38)	0.83 (0.62 - 1.11)	0.78 (0.58 - 1.05)
4	8,773 (22.55)	103 (22.94)	0.93 (0.70 - 1.23)	0.84 (0.63 - 1.11)
5	6,598 (16.96)	74 (16.48)	0.89 (0.65 - 1.21)	0.79 (0.58 - 1.09)

NB Significant factors are highlighted in bold

6.4.2. Study Two: characteristics of patients receiving high dosages of opioid medicine

6.4.2.1. Demographic and physical comorbidity characteristics of patients receiving high dose opioid medication

Patients in the high dose group comprising of new and existing patients newly started on high dose medication, were most likely to be in the oldest age group (≥65 years) (41.81% n=1,731), two thirds were female (66.04% n=2,734) with just over a quarter (28.07% n=1,162) having no physical comorbidity and a quarter having greater than three physical comorbidities (24.49% n=1,014). The highest proportion of patients was in the fourth deprivation (22.73% n=941) quintile with fewer patients in the most deprived (19.30% n=799) or least deprived quintile (15.94% n=660) (Table 30).

New opioid medicine users who became high dose opioid users were more likely to be younger than existing opioid medicine users who received high dose opioids (38.00% new 18-49 years vs 24.31% 18-49 years existing), more likely to be male (37.74% male new vs 33.09% male existing) have fewer comorbidities (20.92% new users greater than three comorbidities vs 25.32% greater than three comorbidities existing) and less likely to be in the lowest deprivation group (15.66% quintile 5 new users vs 20.14 quintile 5 existing) (Table 30).

Table 30 Demographic characteristics of patients who are newly prescribed high dosages of opioid medicines during the study period

Characteristic	All high dose opioid medication users (n=4,140) (%)	Existing opioid medication high dose user (n=3,361)(%)	New opioid medication high dose user (n=779)[1] (%)
Age group (years) at the start 1st high dose quarter			
18-49	1,113 (26.88)	817 (24.31)	296 (38.00)
50-64	1,296 (31.30)	1,085 (32.28)	211 (27.09)
65+	1,731 (41.81)	1,459 (43.41)	272 (34.92)
Gender			
Male	1,406 (33.96)	1,112 (33.09)	294 (37.74)
Female	2,734 (66.04)	2,249 (66.91)	485 (62.26)
Co-morbidities before the start of 1st high dose quarter			
0	1,162 (28.07)	871 (25.91)	291 (37.36)
1	1,135 (27.42)	931 (27.70)	204 (26.19)
2	829 (20.02)	708 (21.07)	121 (15.53)
>3	1,014 (24.49)	851 (25.32)	163 (20.92)
Townsend Deprivation Quintile			
1 (least deprived)	660 (15.94)	517 (15.38)	143 (18.36)
2	844 (20.39)	680 (20.23)	164 (21.05)
3	896 (21.64)	729 (21.69)	167 (21.44)
4	941 (22.73)	758 (22.55)	183 (23.49)
5 (most deprived)	799 (19.30)	677 (20.14)	122 (15.66)

[1]**This number does not equal the number of new users in the first analysis in this chapter (Table 1) as this number includes all patients that received a high dose opioid in not only the first but subsequent episodes of opioid use.**

6.4.2.2. Drug use characteristics of high dose opioid users

Most patients in the cohort had been receiving opioids for greater than five years when they progressed to high opioid dosages (43.55% n=1,803 had been receiving opioids for over five years before progressing) due to existing opioid medicine users having to have two years of no high dose opioid use before their first prescription in 2009. The majority of patients (81.18% n=3,361) starting high dose opioid medication were existing opioid medicine users rather than patients who had started opioid medication in 2009 (new opioid medicine users) (18.82% n=779). Only a minority of patients had received prescriptions for enough weak opioid and/or tramadol to be deemed high dose patients (12.95%) with the remainder receiving at least one type of strong opioid alone or in combination with other opioids (Table 31).

Patients were more likely to be receiving weak opioids or tramadol only or all medications (weak, strong and tramadol) in the existing patient group (13.89%, n=467) compared to the new opioid user group (8.86%, n=69) (Table 31).

Table 31 Previous usage and types of opioid drug potencies prescribed to high dose opioid medicine users

Characteristic	All users (n=4,140) (%)	Existing users (n=3,361) (%)	New users (n=779) (%)
Time to high dose from start of opioid			
Less than one year	290 (7)	111 (3.3)	179 (22.98)
One to two years	466 (11.26)	286 (8.51)	180 (23.11)
Two to five years	1,581 (38.19)	1,178 (35.05)	403 (51.73)
Over five years	1,803 (43.55)	1,786 (53.14)	17 (2.18)
Potency of drug in 1st high dose quarter			
Weak / tramadol / both	536 (12.95)	467 (13.89)	69 (8.86)
Strong	1,663 (40.17)	1,270 (37.79)	393 (50.45)
Strong plus weak / Strong plus tramadol / all	1,941 (46.88)	1,624 (48.32)	317 (40.69)

6.4.2.3. Psychological characteristics and antidepressant and benzodiazepine use in patients prescribed high dose opioid medicines (sum of >120mg OMEQ/day)

Almost three quarters of patients (73.33% n=3,036) had been coded as having a symptom or diagnosis of anxiety or depression at some point in their medical history. This was more common in the younger patients with 82.75% (n=921) of patients ≤49 years who were prescribed high dosages of opioid medication having been coded as anxious or depressed at some point in their record compared to 63.26% (n=1,095) of patients 65 years and older (Table 32).

Just under half (44.32% n=1,835) of all patients received an antidepressant in the year before or after the start of high dose opioid medicine. The proportion of younger patients

receiving antidepressant medicine was higher: 55.34% (n=616) of patients aged 18-49 years compared to only 33.74% of those patients aged 65 years and older (n=584).

A large proportion (37.47%) (n=1,551) of patients overall received a benzodiazepine and/or anti-anxiety drug within a year of high dose opioid use. Younger patients were also more likely to receive benzodiazepines and/or anti-anxiety drugs in the year before or after starting high dose opioid medication, with half of the patients aged 49 and under receiving a benzodiazepine and/or anti-anxiety drug (49.14% n=547) compared to 30.67% (n=531) of the over 65 years age group (Table 32).

Table 32 Psychological characteristics and antidepressant and benzodiazepine and/or anti-anxiety drug use in patients prescribed high dosages of opioid

Characteristic	All patients (%) (n=4,140)	18-49 years	50-64 years	65 years and over
Read coded at any point with depressed or anxious				
Yes	3,036 (73.33)	921 (82.75)	1,020 (78.70)	1,095 (63.26)
No	1,104 (26.67)	192 (17.25)	276 (21.30)	636 (36.74)
Non TCA non duloxetine antidepressant in year either side start date 1st high dose quarter				
Yes	1,835 (44.32)	616 (55.34)	635 (49.00)	584 (33.74)
No	2,305 (55.68)	497 (44.65)	661 (51.00)	1,147 (66.26)
Benzodiazepine and/or anti-anxiety drug prescribed in year either side start date 1st high dose quarter				
Yes	1,551 (37.47)	547 (49.14)	473 (36.50)	531 (30.67)
No	2,589 (62.54)	566 (50.85)	823 (63.50)	1,200 (69.32)

6.4.2.4. Number of opioid drug types used since opioids first started

The median number of opioid types per patient since the start of their opioid treatment who had over 120mg per day opioid at some point was 4 (IQR 3-5) (Table 33).

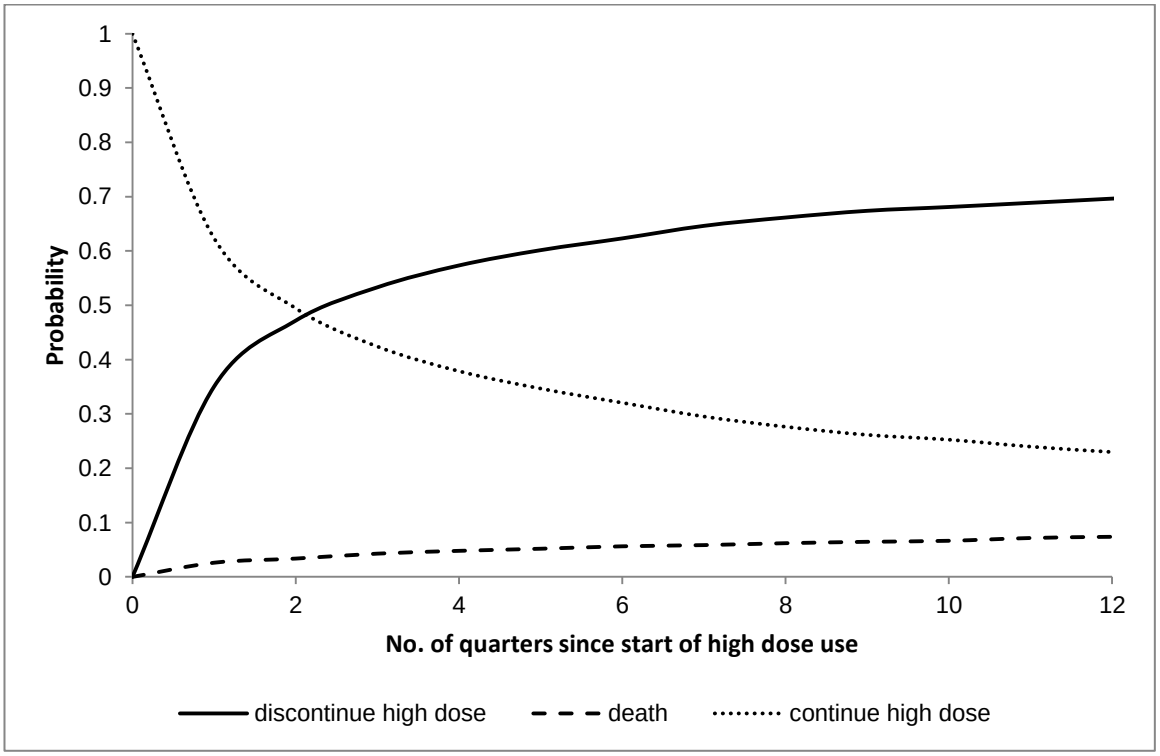
Table 33 Number of opioid drugs received since start of current run by patients initiating high dose opioid therapy during the study period

Number of opioids received since start of treatment	Number of patients (n=4,140) (%)	Cumulative percentage
1	83 (2)	2
2	472 (11.4)	13.41
3	938 (22.66)	36.06
4	1,157 (27.95)	64.01
5	878 (21.21)	85.22
6	416 (10.05)	95.27
7	148 (3.57)	98.84
8	39 (0.94)	99.78
9	9 (0.22)	100

6.4.3. Time to discontinuation of high dose opioid medication

This analysis contained 4,140 patients who started high dose opioid medication in or after the year 2009. Exactly 37.64% of patients do not have a second consecutive high dose quarter due to death or stopping high dose use. Almost one in five patients who had a high dose quarter continued to have a high dose for the next three years (22.98%). Of those patients who have two quarters at a high dosage, just under half (46.67%) continued high dose opioids for at least three years. Almost one in ten patients, 7.38%, died in the three years after starting high dose opioid medication (Figure 13).

Figure 13 Probability of continuation of being prescribed high dosages of opioid medicine in patients newly starting high dose opioid medicines



6.4.4. Analysis of characteristics that influence length of time patients use high dose opioid medicine use

Two characteristics were consistently and strongly associated with long term high dose use: 1) age, with older patients more likely to discontinue high dose (>120mg OMEQ/day) medication than younger patients and 2) the potency of the medication taken by the patient at the start of their high dose quarter, with patients taking strong opioids or strong opioids in combination with weak opioids or tramadol, less likely to discontinue high dose use (Table 34).

Patients in the oldest age group (>65 years) had a faster rate of discontinuation of high dose than younger patients (unadjusted hazard ratio (uHR) 1.24 (1.13-1.36)). This means that overall during follow up, the older group was 1.24 times more likely to discontinue high dose opioid use than the youngest group. The influence of age on discontinuation became

stronger after adjusting for the influence of other variables, with the adjusted hazard ratio (aHR) increased to aHR 1.35 (95% CI 1.20-1.51). After adjustment, the rate of discontinuation between the middle age group 50-64 years compared to the youngest group became significant with an aHR of 1.13 (95% CI 1.02-1.26) (Table 34) .

Patients who started their high dose treatment episode with a weak opioid were more likely to discontinue high dose use that those starting their high dose episode with a strong opioid alone or in combination with other medications (uHR strong vs weak and/or tramadol 0.48 (95 % CI 0.43 - 0.54), uHR strong plus weak and/or tramadol vs weak and/or tramadol, 0.52 (0.47 - 0.58)), this relationship was very slightly attenuated after adjustment for other factors (Table 34).

Another factor associated with longer time to discontinuation of high dose was the having received opioid medication for greater than 5 years. However, this effect changed over time, having less importance at the start of high dose medication use and more importance later on in treatment (Table 34).

Table 34 Characteristics associated with time to discontinuation of high dose opioid medicine use

Characteristic	uHR	aHR
Age group (years)		
18-49	1	1
50-64	1.09 (0.98 - 1.21)	**1.13 (1.02 - 1.26)**
65+	**1.24 (1.13 - 1.36)**	**1.35 (1.20 - 1.51)**
Gender		
Male	1	1
Female	1.05 (0.97 - 1.13)	1.07 (0.98 - 1.16)
Drug potency first high dose quarter		
Weak / tramadol / both	1	1
Strong	**0.48 (0.43 - 0.54)**	**0.46 (0.41 - 0.51)**
Strong and weak / tramadol / both	**0.52 (0.47 - 0.58)**	**0.50 (0.45 - 0.56)**
Number of co-morbidities before first high dose quarter		
0	1	1
1	1.02 (0.92 - 1.13)	0.96 (0.87 - 1.07)
2	1.06 (0.95 - 1.19)	0.98 (0.87 - 1.10)
>3	1.07 (0.96 - 1.19)	0.96 (0.85 - 1.08)
Received an antidepressant in the year before or after first high dose quarter		
No	1	1
Yes year before	0.94 (0.87 - 1.02)	1.02 (0.94 - 1.12)
Yes year after	0.93 (0.81 - 1.08)	1.00 (0.87 - 1.15)
Received a benzodiazepine and/or anti-anxiety drug in year before or after first high dose quarter		
No	1	1
Yes year before	**0.88 (0.80 - 0.96)**	0.92 (0.84 - 1.01)
Yes year after	0.91 (0.79 - 1.05)	0.94 (0.81 - 1.08)

Characteristic	uHR	aHR
Townsend score quintile (patient postcode)		
1	1	1
2	0.99 (0.87 - 1.13)	0.99 (0.87 - 1.13)
3	1.01 (0.89 - 1.15)	1.03 (0.91 - 1.17)
4	1.01 (0.89 - 1.14)	1.03 (0.91 - 1.17)
5	0.98 (0.86 - 1.11)	1.00 (0.88 - 1.15)
Time varying covariate		
Time between start of opioid and high dose		
Less than 365 days		1
≥365 and less than 730 days		1.06 (0.84 - 1.35)
≥730 and less than 1825 days		0.97 (0.79 - 1.20)
≥1825 days		0.99 (0.81 - 1.22)
Time varying		
≥365 and less than 730 days		0.98 (0.94 - 1.04)
≥730 and less than 1825 days		0.97 (0.92 - 1.01)
≥1825 days		**0.94 (0.90 - 0.99)**

NB. A hazard ratio of greater than 1 means a faster rate of discontinuation of high dose

6.5. Discussion

6.5.1. Study One – Characteristics affecting the odds of high dose use

The first study aimed to find the characteristics that are associated with whether a patient is prescribed high dosages of opioid medicines. The study identified that younger patients (under 49 years), patients with physical comorbidities (almost one in four patients in the high dose group had at least three physical comorbidities) and patients who are prescribed antidepressants or benzodiazepines before and after opioid therapy were more likely to be prescribed high dose opioid medication (Table 29).

Doctors may be less likely to increase dosages in older patients as they are wary of adverse effects. A qualitative study which interviewed GPs from one U.K. city (which city was not specified in the paper) found that GPs (n=27) reported that they were more cautious when prescribing strong opioids to older people for joint pain due to the risk of falls and other adverse events [9]. Conversely, prescribers may want to get younger patients back to work as a high priority.

In an Australian prospective cohort study (n=1,500) in which patients taking strong opioids for at least 6 weeks were interviewed at baseline, [110] younger patients were found to have higher levels of depression and poorer coping techniques than older patients, so this may also be the case in the U.K. population. The authors of the Australian study suggest that older patients may be more accepting of pain, though distress due to impaired ability to work may also be contributing to psychological comorbidities in younger patients. Older patients taking opioids were less likely to have sleep problems, poor health, lower pain severity, lower pain interference scores and better self-efficacy scores. This study did not adjust for confounding so this could just be reflecting the different incidence of depression in different age groups.

In the study in this chapter, it is identified that receipt of an antidepressant and benzodiazepine and/or anti-anxiety drug is more common in younger opioid users than older.

Moreover, in the study in this chapter, psychological comorbidities (identified via antidepressant prescribing and potentially benzodiazepine and/or anti-anxiety drug prescribing) are found to be independently associated with high dose use regardless of age thus in the U.K., psychological comorbidity is a key factor affecting the probability of dose increase, regardless of age.

The patients in the high dose group in this study show the high levels of physical and psychological comorbidity that has been described as “adverse selection” (Section 2.9.4) in studies which originate primarily from the U.S.A.. In a commentary discussing the findings of studies in the U.S.A., Sullivan discusses the fact that there is no reason why patients in these particular groups should have a better response to opioid medication per se or require higher dosages of opioid medication. It may be the case that these patients are demonstrating increased pain intensity that could be linked to their anxiety or depression. Sullivan suggests that these patients are “the most distressed” with “the greatest drive for relief” who are prescribed opioids by doctors who “do not know what else to do” [111]. As described in the literature review (Section 2.9), this may be because prescribers are following the WHO pain ladder in an attempt to treat pain and as higher dosages are consumed, it may be that dependence means that it is more difficult to stop consumption due to the effects of withdrawal.

Of particular concern is the relationship between benzodiazepine prescribing and the increased risk of high dose. As discussed in the literature review, receiving a benzodiazepine can be a predictor of probable misuse and of an increased risk of overdose (Section 2.12). In comparison, in a Norwegian study which used dispensing data from all Norwegian pharmacies, 61% of patients receiving greater than 50mg OMEQ/day received a benzodiazepine in the same year [212], a much higher proportion, so concomitant use is common in countries other than the U.K. However, in the Norwegian study, patients had to be receiving this OMEQ dose every day for the full year period (not just 91 days) and so this may not be a direct comparison.

A study from the U.S.A [213], in which patients (n=191) in a multidisciplinary pain treatment facility were interviewed by a doctor, physical therapist and psychologist, found that patients who displayed more signs of distress, suffering and non-verbal communication of pain due to chronic musculoskeletal pain were more likely to be prescribed opioids than those who did not. As patients with high levels of comorbidity were more likely to be prescribed high dose opioid medication, doctors may be more driven to prescribe for patients who are in desperate circumstances. Unfortunately these patients may be more likely to suffer adverse effects from drug interactions or disease interactions (Section 2.8.1). An alternative explanation would be that doctors are treating non-cancer palliative conditions with high dosages. Further work observing consultations in the U.K. in which opioids were prescribed would be needed to confirm this potential association between non-verbal communication and distress. This type of research may be useful for training of prescribers and other health care practitioners to discuss and develop ways of managing patients in distress other than prescribing of opioid medicines. The results of the study imply that adverse selection may be occurring in terms of those patients who reach high dosages and that some patients could possibly be taking high dosages inappropriately. Therefore, it is imperative to check that these patients are benefiting from this medication and that health care practitioners have the necessary training and referral options to be able to manage these patients.

As no other studies in the U.K. have looked at the association between patient characteristics and high dose use, comparisons can only be made with those studies that look at strong opioid use as a proxy for high dose use. Two other studies [27, 28], using different primary care populations in the U.K., found associations between age and use of strong opioids. Ruscitto [28] found that older patients were more likely to be prescribed strong opioids. However, the Ruscitto study is likely to be identifying that older people are more likely to receive opioids for chronic pain as the control group was all patients including patients without pain. The Foy [27] study only included patients that were prescribed opioids and found that younger men and older women were most likely to receive strong opioids. As

the Foy study grouped patients based on age and gender it is difficult to compare with the study within this chapter.

These studies [27, 28] also found very strong associations with number of prescriptions for other non-opioid medicines and receipt of strong opioids. It is possible that polypharmacy is associated with a number of conditions, however, extra medications may be used to treat extra symptoms of a particular disease or patients may be more likely to be using multiple medications for the same disease. In the study in this chapter, no significant association was found with the number of co-morbidities and long-term high dose use, though having greater than three comorbidities was associated with an increased risk of high dose. Potentially, it may be the case that the number of conditions included within this study, as only QOF conditions are included, do not cover the range of long-term conditions for which these extra medications are prescribed. It may also be the case that patients who use long-term high dose medication use more medicines per condition or that patients who use long-term high dose medication use multiple medications to treat symptoms rather than to treat individual long-term conditions. Further analysis of the types of medications in relation to the number of diseases (diseases included and excluded in QOF) used by patients that take long-term high dose medications would provide an insight into this relationship. This may be useful research to see whether these patients are being treated as palliative patients or whether certain types of patients are more likely to use more medicines for the same condition.

6.5.2. Study Two - Proportion of patients continuing high dose medicines and characteristics associated with long-term high dose opioid medicine use

6.5.2.1. Characteristics of patients prescribed high dose opioid medicine (new and existing opioid medication users)

A higher proportion of patients within the youngest age group were prescribed high dosages of opioid medicine compared to older age groups. However, overall, the group of patients receiving higher dosages of opioids included a greater proportion of older patients (41.81%

>65 years) who were women (66.04%). Patients were likely to have at least one comorbidity with a high proportion (24.49%) having at least three comorbidities. This is of concern because these patients are different from patients who are recruited or studied in clinical trials (Section 2.6) and hence opioids maybe have different effectiveness or adverse events in this group. For example older patients may have renal impairment which can increase the probability of adverse events and also adverse effects may have greater consequences in this group, for example if they were to fall (Section 2.8.1).

The proportion of patients who were depressed or anxious varied with age group, with younger patients (≤ 49 years) being more likely to be Read coded with depression or anxiety symptoms or diagnoses. The “Opioids Aware” guidelines [69] recommend that patients have “a very detailed assessment of the many emotional influences of the pain experience”. As such a high number of patients (especially in the younger groups) are Read coded as having depression or anxiety, it may be argued that prescribers are aware of the emotional influences of pain yet lack the training and/or resources to be able to resolve these issues.

In Study 2 in this chapter, 37.47% received a benzodiazepine in the same year as their first high dose prescription with 49.14% of patients receiving a benzodiazepine in the youngest group (18-49 years). Thus, prescribing of benzodiazepines is common in patients who receive high dosages of opioid medicines in the U.K. Although benzodiazepines are prescribed to treat pain, in practice [40], for example in the treatment of muscular spasm in back pain, there is a lack of evidence that this is beneficial [136]. NICE have suggested in their back pain guidelines [136] that there is a need for more evidence of the clinical and cost effectiveness of the use of benzodiazepines in acute back pain. As this is fairly common practice in patients receiving high dose opioid medication it is imperative that a study of the benefits of using these medications over other treatments is conducted and that the results of these trials are implemented in practice. This is because patients may be being treated with opioids where benzodiazepines are more effective (or vice versa) and without good quality evidence, it is difficult to make judgements as to which drugs to prescribe to provide the most effective pain relief. Further work should be conducted to see how patients use

these drugs together and to see how combinations and dosages of these drugs are associated with adverse events and whether the benefits in terms of pain relief are worth these risks from the patient's perspective. Further work should also be conducted as to whether concomitant benzodiazepine use is a flag for misuse in the U.K. as this combination could be used to prioritise patients for review.

6.5.2.2. Factors associated with continuation of high dose opioid medication

Only a small proportion of the patients who started high dose opioid medicines continued to be prescribed high dose opioid medicines for 3 years (22.98%). However, once these patients had been receiving high dose opioids medicines for at least 2 quarters, they had a 50% probability of continuing for the next two and a half years. This is a long time to be exposed to high dosages of opioid medicine and further work is required to establish the benefits and risks associated with sustained high dose use.

Factors that were associated with continuation of high dose opioid medication were young age, the drug type used and having received opioids for longer periods before high dose use started (though this effect changed over time, having a greater influence as time since high dose increased). It is worth noting that the highest proportion of high dose patients were in the age range of older than 65 years old, so a significant number of older patients will continue high dose opioid therapy even if the rate of discontinuation is higher than in younger patients. There may be a number of reasons for the association between discontinuation and older age. The reason for the higher rate of discontinuation is linked to implications of the findings as detailed below.

Older patients who are prescribed high dosages of opioid medicines may be more likely to experience adverse events. This is due to the fact that they have decreased hepatic and renal clearance which prolongs the effect of opioids via reduced clearance and accumulation of parent compounds and metabolites [214]. Older patients may also be more prone to constipation which is the reason why many patients stop opioid medicines (Section 2.11.2.1). Another potential reason why older patients are more likely to stop opioid medicines is

because they are more likely to come into contact with health care professionals or be admitted to hospital which may provide more opportunities for review. A small study, in only one GP practice in the U.K., found that older people are more likely to undergo medication reviews because of the number of medications they are prescribed and so older people may be more likely to be monitored for adverse events or lack of benefit [124]. Further work could be conducted to see what events are associated with stopping opioid medicines, for example, whether a GP consultation or hospital admission occurs at the same time as opioid cessation. It is interesting to see how the prescription of an antidepressant or benzodiazepine at the same time as high dose does not predict continuation of a high dose use in adjusted analysis. This may be because other factors such as adverse events are more dominant in the decision to continue high dose use.

Previous use of opioid medicine, if it was for greater than 5 years, did affect the probability of continuation of high dose in a time dependent manner. So, at the start of high dose treatment patients who had been prescribed opioid medicines for at least 5 years prior to high dose use starting were just as likely to stop high dose treatment as patients being prescribed opioids for fewer than 5 years. However, as time since start of high dose opioid use increased, these patients were less likely to stop being prescribed high dose opioid treatment. This could be because at the start of high dose use other factors are more likely to affect whether a patient continues high dose usage, for example adverse events, lack of effect or an alternative treatment is used. However, after this period of time, the fact that patients have been receiving opioids for many years before high dose use does affect the probability of continuation. This means that patients with a long history of opioid use (and chronic pain) should have a careful evaluation of the effectiveness of high dose use in order to establish whether they are receiving effective pain relief as they are likely to continue to receive opioids for long periods.

6.5.3. Strengths and limitations

This analysis of patients who were using opioid medication involved a calculation of the dosage of the opioid that a patient was prescribed. This is novel as no other studies in the U.K. have calculated the dosage that a patient receives and linked this with physical and psychological patient characteristics. The cohort used was from data from multiple regions of England and for all types of pain condition. Both Read Codes for anxiety and depression and prescribing of antidepressants and benzodiazepines were included to ensure identification of patients with these conditions and psychological comorbidity was approximated before opioid use started to try to rule out opioid induced depression or depression from long term pain.

However, there are a number of limitations that should be considered when evaluating the importance of the results of this study and the implications of the results for future practice and research as described below.

Using the method described to calculate dosage, the dosage could be overestimated as multiple drugs could be prescribed in the same month if the prescriber decides that the patient would benefit from opioid rotation. In this case, the prescriber may never have intended for the patient to continue to take the two opioids at the same time. However, because the patient was required to have received greater than 120mg OMEQ/day for at least 91 days, the overlap would have to be for a significant proportion of this time period.

Another limitation of the first study is that only patients who started an opioid medication in 2009 were included in the analysis whereas in the analysis of patients who start high dose use at some point (Study 2), half of patients who were receiving opioids for at least five years beforehand. This could be related to the fact that patients in the existing group had to have 2 years in which they did not receive high dose. This means that the patients receiving high dosages in this study could be more likely to be patients who increase the dosage used at a faster pace than other opioid medicine users. However, the two year time period was introduced to ensure patients were new users of high dose opioid medicine.

Some of the patients in the original data were excluded because they were not from linked practices and so did not have a deprivation score. However, when all other characteristics of the patients were compared between these groups, they showed no statistically significant differences.

This analysis only considered the relationship between patient characteristics and high dose use in the first episode of opioid use within the study period. It is possible that patients with certain characteristics are more likely to receive high dose opioid medication in their future use of opioids. Additionally it is possible that patients have several episodes of high dose use other than their first episode. Whether this is the case was beyond the limits of this study and should be examined in future research.

6.5.4. Summary

The study conducted in this chapter has identified that patient characteristics, for instance depression (defined as being prescribed an antidepressant at the start of opioid medicine use), are associated with an increase in the probability of being prescribed a high dose of opioid medication in new users of opioid medicines. This is mainly because patients who are depressed at the start of opioid medicine use are more likely to increase to high dose use rather than these patients being more likely to continue high dose use. These results highlight the possibility of “adverse selection” of users of opioid medicines. This information is useful as it means that targeting interventions to prevent high dose use in depressed patients may be a future avenue for research and may also highlight patients for prescribers to monitor closely when starting opioid medication.

Also of note was the difference in the probability that patients had a Read Code for depression or anxiety at any point in their records based upon age group, with 82.75 % of patients ≤ 49 years having been coded with a depression or anxiety diagnosis at some point compared to 63.26% in the oldest group. This may highlight that younger patients are likely to have psychological comorbidity and audits of psychological treatments offered to them throughout their course of treatment are required. However, the effect of depression

appeared to be independent of age, meaning that all patients should be screened for symptoms of psychological comorbidity.

Another important result from this chapter is the high proportion of patients who also receive benzodiazepines at the same time as a high dose opioid of opioids. Again, a difference in age was seen in that half of the patients in the younger age group (≤ 49 years) who received a high dose opioid also received a benzodiazepine at least in the year before or after high dose use. The number of older patients (>65 years) who also received a benzodiazepine was also fairly high at 30.67%. This may reflect the fact that younger patients have painful conditions that are more likely to be treated with benzodiazepines but it also means this group is at greater risk of adverse events associated with opioid use.

Chapter 7. General discussion and implications for research, practice and policy

7.1. Discussion of the aims and objectives of the thesis

This thesis set out to measure long-term and high dose opioid use in primary care and to see how patient characteristics were associated with how opioid use develops over time. This section discusses whether the results met the aims and objectives of the thesis.

7.1.1. Patients continuing to be prescribed opioid medicine over long periods

An estimated 10.58% of the U.K. population were prescribed at least one opioid prescription every year in the U.K. for non-cancer pain (Section 3.5.1). Though many patients are only prescribed opioids for a short period, an estimated one in thirty (3.00%) people in the U.K. population received opioid medicines for greater than one year from their first opioid prescription in 2009 (this figure includes new and existing users).

Of the new users of opioid medicines, only a small proportion of these patients continue to be prescribed opioid medicines (with no gap) in the long term. The proportion of patients newly starting treatment who have continuous prescribing for at least one year is 5.75%, however, two thirds of these patients continue for at least one more year (63.30%). Of these patients, 56.59% continue until the end of the five years (Section 4.4.2).

From this study, it cannot be determined whether patients receiving opioids in the long-term continue to receive the benefits associated with opioid treatment in terms of decreased pain intensities and improved quality of life. However, from the results of observational studies in other countries and via concerns raised by pain specialists, there is a suggestion that there may be a large number of patients who could potentially benefit from a review of their opioid treatment.

Patients who were female, received an antidepressant in the year before opioid use started and were younger, were less likely to discontinue long-term opioid use. Unless patients with these characteristics are more likely to obtain benefits from the use of opioid medicines or that these patients are more likely to have long-term pain, it is possible that they are being adversely selected for long-term opioid use.

7.1.2. Number of patients prescribed high dosages of opioid medicines for at least 91 days

At least one in hundred people in the U.K. population who were prescribed an opioid were prescribed a high dose opioid in their first quarter of use in the year 2009. This group of patients is a mixture of new and existing patients receiving opioid medicines with the vast majority (98.11%) being existing users of opioid medicines (Section 5.4.2.1). To be considered a high dose opioid medicine user, a patient needed to receive more than 120mg OMEQ/day averaged over a 91 day period. These can therefore be considered long-term high dose patients. Only a small number of patients in the new users of opioid medicines group received high dosages for greater than 120mg OMEQ/day in the first episode of use. However, it was also found that large numbers of existing users started high dose after greater than 5 years of use so this may be due to insufficient time in the study. The results of this study show that it is important to not just focus on new users as this misses out many of the worst patients.

The probability of continuation is higher in patients receiving opioids for longer and at higher dosages. For example, patients who received over 10mg OMEQ/day for over two years, over half continued to receive opioid medicines for the next five years. These simple estimates based on the length of usage and dosage may be useful for health care practitioners and patients to discuss when evaluating future care.

In a group of chronic pain patients, which was defined as at least two quarters of opioid use, patients starting opioid medicines who were younger (aged 18-49), had 3 or more comorbidities or in receipt of an antidepressant or benzodiazepine before or after opioid use started were more likely to receive high dosages of opioid medicines. These are not reasons why a patient should respond better to opioid medicines and so may be a sign that these patients are also being adversely selected for high dose treatment.

Although the odds of high dose use were greater in younger patients, most patients receiving high dosages were aged over 65+ years. Younger patients were more likely to have ever

been diagnosed as depressed or anxious, to be receiving an antidepressant or a benzodiazepine or other anti-anxiety drug.

Of the patients that were prescribed high dosages of opioid medicines for at least 91 days, 37.64% of patients did not have a second consecutive high dose quarter due to death or stopping high dose use. Almost one in five patients who had a high dose quarter continued to have a high dose for the next three years (22.98%). Older patients, patients prescribed weak opioids and/or tramadol discontinued high dose use at a faster rate than younger patients. Therefore, once patients had been using high dose opioids for a longer period, they were likely to continue to receive high dosages in the long-term.

7.1.3. Effect of age on long-term and high dose opioid use

Although the vast majority of patients were older, a higher proportion of patients in the youngest categories were likely to continue long-term use (after 2 years) and receive higher dosages. There is a clear difference in age groups associated with the ways patients receive opioid medicines. This may be because patients have different painful conditions at different ages and the associated stress of unemployment or expectations of normal in younger patients, however it may also flag that younger patients need further support to manage their chronic pain with opioid medicines. This means that interventions may need to be tailored to the specific needs of different types of patients.

7.1.4. Effect of psychological comorbidity

It has been identified that factors such as patient's psychological comorbidities have been found to influence a patient's use of opioid medicines. This may mean that in some cases opioid medicine use is prolonged or patients are exposed to higher dosages than is necessary because if the depression or anxiety was treated more effectively then patients would have better outcomes. For example, the Scottish Intercollegiate Guideline Network (SIGN) guidelines for chronic pain [22] recommend, based on a good quality randomised controlled trial [215], that patients with depression should be offered antidepressant therapy. However, the original randomised controlled trial incorporated six sessions of self-

management, therefore antidepressant prescribing alone may not be enough to help these patients [215]. Patients with psychological comorbidities were identified in this study via antidepressant prescribing. Investigations into the way in which this group are treated could have benefits for these patients due to the particular interaction of pain and depression.

7.2. Strengths and weaknesses of the thesis

This thesis had a number of strengths. For example, a key strength was that patient level data was used. This meant that prescriptions could be attributed to individual patients and due to the comprehensive nature of the database these prescription patterns could be linked to patient individual patient characteristics, rather than just looking at associations between opioid prescribing and population characteristics.

In addition, patient characteristics, (specifically comorbidities such as anxiety and depression), were measured before opioid use was started. This meant that the influence of these characteristics could be seen separately from the effect of taking an opioid, for example, in previous studies anxiety and depression were found to be associated with long-term and high dose opioid use. This may have been because the opioid or long-term painful condition was causing the depression. However, this study has shown that anxiety or depression before opioid use even starts potentially predisposes the patient to long-term or high dose opioid medicine use.

Also, the study was conducted using a large sample of patients, from multiple surgeries and multiple regions. This reduces the likelihood (though does not prevent) type II error (that the null hypothesis is true). The data used to calculate the probabilities within this thesis is likely to be reliable because of the fact that prescriptions are usually generated via computer and this data is generated as a result of this process. The data was also collected during routine patient care; prescribers were not aware of the specific research that would be conducted on the data and so this would have not influenced the way that they treated patients.

A further strength of this study was that the dosages consumed by patients were also calculated. Previous research in the U.K. has linked patient characteristics with the prescribing of certain types of opioid e.g. ‘strong opioids’ however characteristics of patients have not be linked to estimated dosages consumed which can vary to a great extent.

However, there are also a number of limitations that apply to this thesis.

This thesis only examined the factors associated with the first episode of opioid use. It is possible that patients are likely to receive several episodes of opioid use due to the recurrent nature of chronic pain [216]. It is possible that prescribers may be more reluctant to prescribe long-term or high dose opioid medicines to patients (with certain characteristics) in their first episode of use, however as the patient continues to present they may be more likely to continue to prescribe in the long term. Looking at the probability of future use would provide further information about how one episode fits in with total use and whether the relationship between factors and long-term and high dose use changed in subsequent episodes.

Within this thesis patients that had had a cancer diagnosis at any point in their record were excluded. This was because previous studies have excluded patients that received opioids for cancer conditions due to the fact opioid treatment for cancer pain was possibly for palliative reasons. However, as cancer survival rates increase, it is likely that long-term opioid use may also be of concern in this particular group and so research into opioid use in this particular group may be beneficial. Also, by removing patients that have a cancer diagnosis at any point in their record this will remove patients that have been taking opioids for non-cancer conditions before they develop cancer. This was done because coding of the cancer condition may be delayed and it would have been difficult to judge which patients were truly prescribed opioids for non-cancer conditions. It may also be the case that the fact a patient becomes a cancer patient may influence whether or not a prescriber decides whether they should continue long-term or begin or continue high dose opioid medicine use.

An additional limitation is the fact that it was not possible to link the type of pain and the chronicity of the condition with the probability of long-term and high dose use. It is possible that the factors found to be associated with long-term and high dose use are just the factors that are associated with certain types of chronic pain (compared to factors associated with other painful conditions). However, a long period of use (2 years) was used to define long-term use and for the high dose analysis a control group of patients who had received opioid medicines for at least 90 days was used and therefore should have, at least in part, selected for patients with chronic pain.

A further problem is that the data within this thesis relates to what patients were prescribed. From this data it cannot be deduced whether the patient actually consumed these medications or at what dosage they actually consumed these medicines. They may also purchase opioid medicines, “Over the Counter” from a pharmacy as preparations of codeine and dihydrocodeine are available. This may mean that opioid use is underestimated if patients continue to buy opioid medicines over the counter or overestimated if patients do not consume the medication that they have been prescribed. Furthermore, it is possible that certain groups of patients, with certain characteristics could be more likely to order more opioid medicine prescriptions but not consume the medication. For example, elderly patients may be more likely to order opioid medicines if they use the repeat dispensing service and their medicine is on repeat however, they may not actually consume the medicine.

7.3. Recommendations

7.3.1. Practice

7.3.1.1. Informing patients of probability of continuation

At the outset and at each stage of opioid treatment, patients should be informed of the probable course of their opioid use (e.g. probability of continuation at 1 year, 2 years etc.) using the results of this thesis. This would allow patients to make more informed decisions about how they would like to manage their chronic pain condition and could potentially prompt patients to evaluate the benefits from opioid treatment. This information could come from prescribers or from other sources such as via pharmacists at the point of dispensing or during medicines use reviews or via other sources such as the media.

Prescribers may also manage patient expectations of opioid treatment at the start of opioid prescribing by agreeing check points for appointments to take place in future when opioids should be reviewed with the patient. This could be done by preventing further issues of opioid medicines after a certain point in time without a review by a prescriber.

7.3.1.2. Review of patients taking opioid medicines

Patients taking opioid medicines (in the long-term and at high dosages) should be reviewed on a regular basis and this review process audited. This review should explore the continued need for opioids. The review process should be documented with the main outcomes of treatment for that patient and whether these outcomes have been achieved and continue to be achieved. This should be documented in the patient's medical record to provide continuity of care. Adverse events associated with the use of opioids should be discussed with the patients and documented in the notes. Reviews could be focused on high risk patients, for example those with a history of anxiety or depression, those using high dosages or those patients who are also receiving benzodiazepines.

7.3.1.3. Coding of patients with chronic pain conditions

Patients with chronic pain conditions should be Read coded as such to enable future audit of the management of patients with chronic pain and to facilitate research into the proportion of chronic pain patients who continue long-term or receive high dose opioid medicine use. An operational definition for chronic pain should be developed to standardise the types of patient who are coded as chronic pain patients. In addition to a chronic pain Read Code the disease or area of the body for which the opioid is prescribed should be coded in order to understand which conditions are associated with long-term or high dose use in an unbiased manner. CPRD should audit whether prescribers are adding indications where they have been advised to do so and report the training that they offer to new prescribers or locums contributing data to CPRD to ensure that the data entered into the system is reliable.

7.3.1.4. Training of prescribers in chronic pain

The results of this work could be disseminated to prescribers to raise awareness of the probability that patients at each stage in their treatment will continue to receive opioid medicines and the fact that patients within certain groups may be more likely to continue opioid use. The combinations of medicines associated with high dose use could also be used to raise awareness of what the dosages of opioids patients are actually taking.

This may in turn highlight the need for further training in the management of chronic pain. Clinical commissioning groups should identify whether the prescribers in their group feel that they require training to manage chronic pain patients or the need could be identified via audit of current practices with regard to controlled drugs (e.g. number of prescriptions issued without review, number of patients receiving high dosages of opioid medicines etc). This training could incorporate how to manage patients at the outset of opioid medicines and the best way to approach conversations about opioid use, for example how to provide the best information to patients to enable them to make a decision around whether to continue opioid medicines or not in the absence of tangible benefits (i.e. improved function) to the patient. This training could incorporate dealing with patients of different age groups, for example

younger women using opioid medicines in the long-term or the best ways to manage chronic pain patients with anxiety or depression. One Canadian author of several opioid studies and pain specialist Dr. David Juurlink, has described, in a recent podcast for the Canadian medical association journal [177], how discussing reducing opioid use in patients is one of the “most difficult conversations in medicine” which takes time and experience. This means that prescribers may benefit from training about how best to speak to patients to allow them to make informed decisions about the benefits of their opioid medicines.

7.3.2. Policy

7.3.2.1. Implement recommendation that patients are reviewed on a yearly basis

The results of this study support the recent suggestion by pain specialists [139] that patients taking opioid medicines should be reviewed at least on a yearly basis. This is because patients who take opioids for at least a year are likely to continue opioid medicines in subsequent years and it is crucial that prescribers monitor patients for evidence that opioids are achieving their goals, that there is an ongoing need for the use of opioids, that monitoring takes place for signs of drug misuse and that patients are monitored for signs of adverse effects.

7.3.2.2. Improvement of guidelines

National guidelines in the U.K. [69] for the use of opioids in chronic pain have been implemented in recent years and provide good advice about how to start opioid medicines. However, within these guidelines there is a lack of information about how opioid use should develop over time, for example the situations in which patients should receive immediate and modified release preparations or when opioids should or should not be combined. This may be due to a lack of research into the benefits of combinations of opioids and the situations where this may be appropriate. Therefore research should be conducted as to where these combinations are inappropriate.

Additionally, high dose use is more common in patients with anxiety and depression; although the current guidelines flag the need for cautious prescribing of opioids when patients have comorbid psychological conditions, there are no recommendations of how to manage patients with these comorbidities. National standards for the treatment of patients at risk of high dosages or long-term therapy could be implemented to improve the care of these patients or provide prescribers with a tool to audit the treatments that are available to their patients.

7.3.3. Research

7.3.3.1. Discussion of the results of this thesis with patients and prescribers

Research should be conducted to discuss with patients and prescribers the results of this study and how this may impact on their practice and the likelihood that they will continue opioid medicine use, be this positive or negative. The results of the study could be used as a tool (and compared to other tools) to discuss the problems or benefits associated with opioid usage with prescribers to help to guide avenues of future research.

7.3.3.2. Alternative treatments available for patients to access

As this study only measures the length and dosages used by patients it is not possible to know what other chronic pain treatments have been tried by GPs and how opioid treatment fits into the patient's treatment plan. Future research should involve an audit, using data extracted directly from GP computer systems, including free text data, as to the types of treatment patients have been given or offered and the types of treatment available for prescribers to refer to. How this relates to what is documented on the patient record, and if this is integrated into the patient's future plan to treat their pain, could also be reviewed.

If patients have visited the pain clinic, then the recommendations and treatments received from the pain clinic should be audited to see how this influences the course of opioid treatment.

7.3.3.3. Audit of outcomes of patients taking opioid medicines

As this study did not measure outcomes in terms of day to day quality of life for patients receiving opioid therapy in the community, further work should be undertaken to measure outcomes for patients taking opioids at each stage of treatment. For example, a measure should be taken of whether when opioid use was started, whether patients set goals and how opioid use was helping them to achieve these goals and whether these goals are still being met at subsequent time points.

Future research should involve asking patients how they understand their medication use (for example the temporal nature of their pain and how this relates to when they use immediate release preparations) and using the results of this study as a discussion point, for example in patients starting to take opioid medicines whether they are happy to continue to receive opioid medicines for long periods and as to how and when they use their opioid medicines in combination and their understanding of these combinations and how this contributes to the increase in dosages received. This research could be directed to the specific patient groups that were identified as being more likely to receive long-term or high dose opioid medicines, for example in depressed younger patients.

7.3.3.4. Pharmacist interventions into opioid prescribing

The General Practice Forward View initiative has committed to supplying funding for nearly 2,000 extra pharmacists to work within surgeries in England [217]. This means that pharmacists are ideally placed to influence prescribing. A previous small RCT has identified that pharmacist prescribing can lead to improvements. Prescribers who took part in the trial only accepted 60% of the pharmacist recommendations and some comments from GPs were negative such as pharmacists were “tinkering around the edges”. In order for pharmacists to have a greater impact, it may be that they need more training in the area of pain management, with examples of how other pharmacists have been able to make changes that have been of the most benefit to patients.

Pharmacists in their role as medicines management advisors within CCGs can be involved in the monitoring of patients receiving opioid medicines. As initiatives to change prescribing may differ from one CCG to another, it is important that research is conducted into the best ways that pharmacists can influence prescribing to reduce long-term or high dose use and to understand what barriers and facilitators need to be overcome or in place in order to make successful changes. This could incorporate staffing levels required to deliver interventions, training requirements for pharmacists to be able to deliver effective interventions, the actual interventions that have been successful and whether the same interventions achieve the same goals within other areas of the U.K..

7.3.3.5. Determining the cost effectiveness of interventions to reduce opioid prescribing

This study identified that patients were receiving many different drugs at a range of dosages. As patients are using lots of different opioid drugs at a range of dosages, it may be the case that intervening with certain types of patients may be more likely to achieve good outcomes for patients. As there are so many more patients who take opioids at lower dosages, it may be the case that interventions in this group may be as cost effective as those made for patients at higher dosages. Further work should be conducted as to what exact interventions are most effective in specific groups.

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Appendix 1 Outline of analyses

Figure 14 Outline of analysis in Chapters 3 and 4

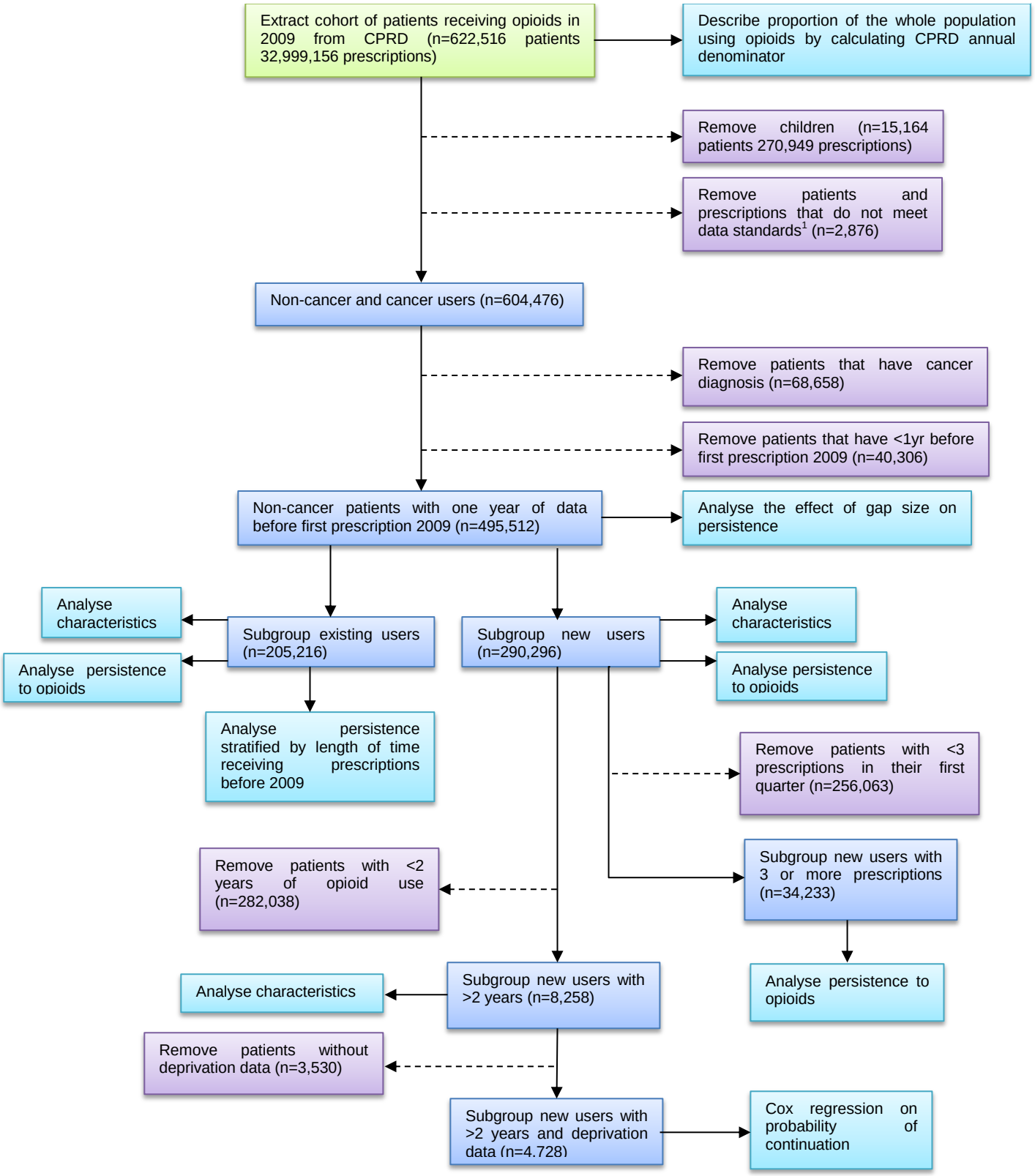
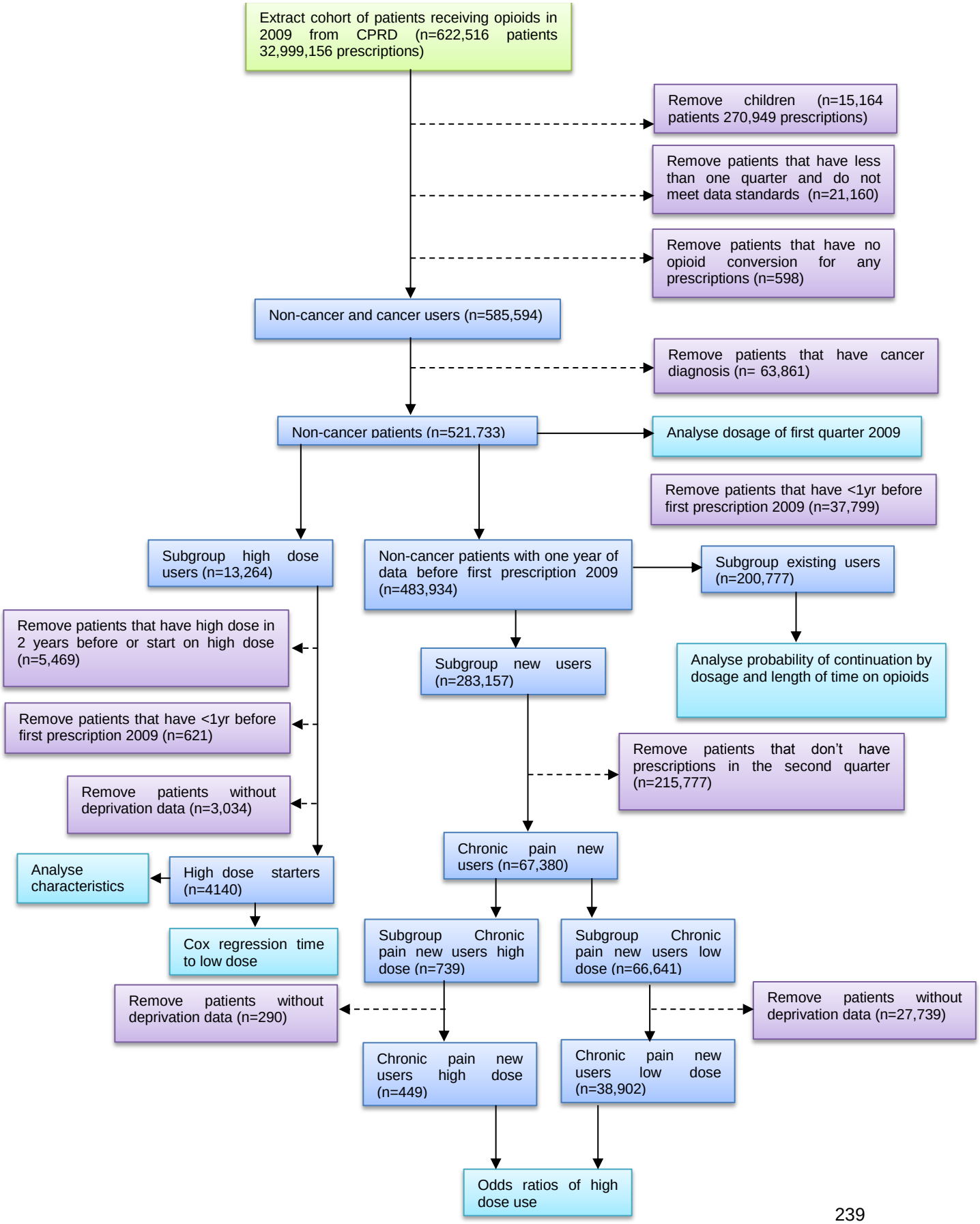


Figure 15 Outline of analyses in Chapters 5 and 6



Appendix 2 Opioid product codes

prodcode	Product name
4	Co-proxamol 32.5mg/325mg tablets
11	Co-dydramol 10mg/500mg tablets
19	Co-codamol 8mg/500mg tablets
53	Dihydrocodeine 30mg tablets
57	Co-codamol 8mg/500mg effervescent tablets
86	Tramadol 50mg capsules
96	Co-codamol 30mg/500mg tablets
124	Distalgesic 32.5mg/325mg tablets (Meda Pharmaceuticals Ltd)
142	CODEINE SOLUBLE TAB
158	Codeine 30mg tablets
187	Zydol 50mg capsules (Grunenthal Ltd)
191	Dihydrocodeine 10mg/5ml oral solution
203	CODEINE CO SOLUBLE TAB
213	Codeine 25mg/5ml oral solution
234	Pethidine 25mg tablet
241	CODEINE CO TAB
306	Aspirin with codeine phosphate and caffeine tablets
328	Pentazocine 50mg capsules
382	Codeine 15mg tablets
396	Buprenorphine 200microgram sublingual tablets sugar free
483	Co-proxamol (dextropropoxyphene and paracetamol) 32.5mg with 325mg/5ml oral suspension sugar free
495	MST Continus 10mg tablets (Napp Pharmaceuticals Ltd)
539	Codeine 60mg tablets
607	MST Continus Suspension 20mg granules sachets (Napp Pharmaceuticals Ltd)
620	Fentanyl 25micrograms/hour transdermal patches

prodcode	Product name
625	Co-codamol 8mg/500mg capsules
655	Morphine sulfate 10mg/5ml oral solution unit dose vials sugar free
656	Tylex 30mg/500mg capsules (UCB Pharma Ltd)
685	Aspav dispersible tablets (Actavis UK Ltd)
687	Tramacet 37.5mg/325mg tablets (Grunenthal Ltd)
701	Tramadol 50mg modified-release capsules
748	Durogesic 25micrograms transdermal patches (Janssen-Cilag Ltd)
757	Fentanyl 50micrograms/hour transdermal patches
767	Solpadol 30mg/500mg capsules (Sanofi)
800	Co-codamol 30mg/500mg capsules
810	Co-codamol 30mg/500mg effervescent tablets
1261	Co-codamol 30mg/500mg effervescent powder sachets sugar free
1503	Oramorph 10mg/5ml oral solution (Boehringer Ingelheim Ltd)
1527	Migraleve tablets (McNeil Products Ltd)
1616	Migraleve Pink tablets (McNeil Products Ltd)
1640	Kapake 30mg/500mg tablets (Galen Ltd)
1708	Codafen Continus tablets (Napp Pharmaceuticals Ltd)
1762	Dextropropoxyphene HCl with paracetamol 32.5mg with 325mg tablets
2040	Remedeine tablets (Crescent Pharma Ltd)
2041	Dihydrocodeine 60mg modified-release tablets
2047	Co-codaprin 8mg with 400mg tablets
2211	Solpadol 30mg/500mg effervescent tablets (Sanofi)
2250	CODEINE & PARACETAMOL TAB
2367	Pentazocine 25mg tablets
2450	Pethidine 50mg tablets
2462	Cosalgesic Tablet (Actavis UK Ltd)
2555	Dihydrocodeine with paracetamol 10mg+500mg tablets
2698	CODEINE & PARACETAMOL 8 MG TAB

prodcode	Product name
2794	Co-codamol 30mg/500mg tablets (Wockhardt UK Ltd)
2846	Paracetamol 500mg with codeine phosphate 30mg effervescent tablet
2917	Paracetamol 500mg with codeine phosphate 30 mg tablet
2957	MST Continus 30mg tablets (Napp Pharmaceuticals Ltd)
2986	Co-codaprin 8mg/400mg dispersible tablets
2988	CODEINE PHOSPHATE 15 MG ELI
2997	Oramorph sr 10mg Tablet (Boehringer Ingelheim Ltd)
2998	PARACETAM/DYHYDROCODEINE(500MG/30MG) MG TAB
3029	CO-CODAMOL EFF 30MG/500MG TAB
3064	Buprenorphine 400microgram sublingual tablets sugar free
3156	Solpadol 30mg/500mg caplets (Sanofi)
3185	Paracetamol 500mg with codeine phosphate 30mg capsule
3239	Meptazinol 200mg tablets
3272	PARACETAM/DYHYDROCODEINE(500MG/20MG) TAB
3378	Tramadol 50mg soluble tablets sugar free
3435	Tylex 30mg/500mg effervescent tablets (UCB Pharma Ltd)
3522	Temgesic 200microgram sublingual tablets (RB Pharmaceuticals Ltd)
3644	Zydol SR 100mg tablets (Grunenthal Ltd)
3698	Df118 40mg Tablet (Martindale Pharmaceuticals Ltd)
3713	Medocodene Tablet (Manufacturer unknown)
3714	DEXTROPROPOXYPHENE NAPSYLATE/PARACETAMOL MG TAB
3724	Migraleve Yellow tablets (McNeil Products Ltd)
3919	Sevredol 10mg tablets (Napp Pharmaceuticals Ltd)
3990	Dextromoramide 5mg tablets
4114	Tramadol 100mg modified-release capsules
4115	Tramadol 100mg modified-release tablets
4236	Palfium 5mg tablets (Roche Products Ltd)
4266	Morphine 10mg tablets

prodcode	Product name
4280	MST Continus 5mg tablets (Napp Pharmaceuticals Ltd)
4349	PARACETAMOL & CODEINE TAB
4476	MST Continus Suspension 60mg granules sachets (Napp Pharmaceuticals Ltd)
4477	MST Continus 60mg tablets (Napp Pharmaceuticals Ltd)
4487	CAFFEINE CITRATE/CODEINE PHOSPHATE/PARAC 15 MG TAB
4518	DF 118 30 MG TAB
4556	Paramol tablets (SSL International Plc)
4607	Co-proxamol 32.5/325 Tablet (Dista Products Ltd)
4671	Codeine phosphate 30mg with Paracetamol 500mg capsules
4691	Fentanyl 100micrograms/hour transdermal patches
4693	Oramorph 10mg/5ml oral solution unit dose vials (Boehringer Ingelheim Ltd)
4718	Migraleve - 1 Tablet (Pfizer Consumer Healthcare Ltd)
4823	Dihydrocodeine 40mg tablets
4834	Tramadol 150mg modified-release capsules
4950	Dihydrocodeine with paracetamol 30mg+500mg tablets
4999	Tramadol 24 Modified-release tablet
5028	Tramadol 24 Modified-release tablet
5048	Durogesic 50micrograms transdermal patches (Janssen-Cilag Ltd)
5137	Hydromorphone 2.6mg capsules
5138	Hydromorphone 1.3mg capsules
5169	Zydol SR 200mg tablets (Grunenthal Ltd)
5257	Tramadol 12 Modified-release tablet
5498	Propain caplet (Sankyo Pharma UK Ltd)
5555	Sevredol 10mg/5ml oral solution (Napp Pharmaceuticals Ltd)
5563	Morphine sulphate 12 20mg Modified-release capsule
5585	Oxycodone 10mg capsules
5599	OxyContin 10mg modified-release tablets (Napp Pharmaceuticals Ltd)
5651	Fentanyl 400microgram lozenges

prodcode	Product name
5652	Morphine sulphate 12 50mg Modified-release capsule
5657	Durogesic 75micrograms transdermal patches (Janssen-Cilag Ltd)
5681	Morphine 10mg modified-release tablets
5685	Syndol easy to swallow Tablet (SSL International Plc)
5696	Fentanyl 600microgram lozenges
5697	Fentanyl 800microgram lozenges
5714	MST Continus 15mg tablets (Napp Pharmaceuticals Ltd)
5840	Morphine sulfate 10mg/5ml oral solution
5843	Oxycodone 10mg modified-release tablets
5936	Transtec 35micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
5955	Paracetamol 500mg / Dihydrocodeine 30mg tablets
5991	MST Continus 100mg tablets (Napp Pharmaceuticals Ltd)
6002	Morphine 10mg modified-release capsules
6040	Transtec 52.5micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
6153	Zydol SR 150mg tablets (Grunenthal Ltd)
6181	Transtec 70micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
6215	Tramadol 200mg modified-release capsules
6226	Aspirin 500mg / Papaveretum 7.71mg dispersible tablets sugar free
6232	Sevredol 20mg tablets (Napp Pharmaceuticals Ltd)
6234	Dihydrocodeine 120mg modified-release tablets
6269	Morphine sulfate 20mg/ml oral solution sugar free
6298	Fentanyl 75micrograms/hour transdermal patches
6366	Sevredol 50mg tablets (Napp Pharmaceuticals Ltd)
6557	OxyNorm 5mg capsules (Napp Pharmaceuticals Ltd)
6558	Tramadol 37.5mg / Paracetamol 325mg tablets
6608	Oxycodone 20mg modified-release tablets
6609	Oxycodone 5mg/5ml oral solution sugar free
6665	Paracetamol with codeine & buclizine tablet

prodcode	Product name
6708	Oxycodone 40mg modified-release tablets
6736	Morphine 20mg modified-release granules sachets sugar free
6769	Oxycodone 5mg modified-release tablets
6790	Oxycodone 5mg capsules
6879	Buprenorphine 35micrograms/hour transdermal patches
6886	Codeine phosphate 30mg with paracetamol 500mg tablets
6917	Buprenorphine 52.5micrograms/hour transdermal patches
6948	Oxycodone 80mg modified-release tablets
7063	Co-dydramol 10mg/500mg/5ml oral suspension
7072	Co-codamol 15mg/500mg tablets
7082	Durogesic DTrans 25micrograms transdermal patches (Janssen-Cilag Ltd)
7104	Kapake 30mg/500mg effervescent tablets (Galen Ltd)
7107	Durogesic DTrans 50micrograms transdermal patches (Janssen-Cilag Ltd)
7126	Fentanyl 12micrograms/hour transdermal patches
7167	OxyContin 5mg modified-release tablets (Napp Pharmaceuticals Ltd)
7197	Morphine sulphate 12 30mg Modified-release capsule
7236	Buprenorphine 10micrograms/hour transdermal patches
7238	Buprenorphine 20micrograms/hour transdermal patches
7275	Oxycodone 20mg capsules
7334	Buprenorphine 5micrograms/hour transdermal patches
7372	OxyNorm 20mg capsules (Napp Pharmaceuticals Ltd)
7389	OxyContin 20mg modified-release tablets (Napp Pharmaceuticals Ltd)
7397	Durogesic DTrans 75micrograms transdermal patches (Janssen-Cilag Ltd)
7406	OxyNorm 10mg/ml concentrate oral solution (Napp Pharmaceuticals Ltd)
7450	Pentazocine 15mg with paracetamol 500mg tablet
7469	Df118 10mg/5ml Oral solution (Martindale Pharmaceuticals Ltd)
7499	Calpol extra Tablet (Warner Lambert UK Ltd)
7518	Aspirin 400mg with Codeine 8mg dispersible tablets

prodcode	Product name
7542	Codeine phosphate 8mg with paracetamol 500mg tablets
7555	BuTrans 5micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
7696	PARACETAMOL 500MG/CODEINE 10MG MG TAB
7729	Morphine hcl Oral solution (Thornton and Ross Ltd)
7770	ASPIRIN/CODEINE PHOSPHATE/PARACETAMOL 250 MG TAB
7801	MORPHINE SULPHATE SR 30 MG TAB
7875	Morphine 30mg modified-release tablets
7950	DOLOXENE 65 MG PUL
7976	PARACETAMOL 450MG/CODEINE 8.1MG TAB
7989	DIHYDROCODEINE TARTRATE/ASPIRIN 300 MG TAB
7998	Dextromoramide 10mg tablets
8017	Temgesic 400microgram sublingual tablets (RB Pharmaceuticals Ltd)
8039	MST Continus 200mg tablets (Napp Pharmaceuticals Ltd)
8246	Codeine phosphate 8mg with paracetamol 500mg effervescent tablets
8329	Solpadeine Tablet (GlaxoSmithKline Consumer Healthcare)
8335	Paracodol 8mg/500mg capsules (Bayer Plc)
8375	Fortral 25mg tablets (Zentiva)
8416	Tramadol 12 Modified-release tablet
8447	Meptid 200mg Tablet (Shire Pharmaceuticals Ltd)
8456	DHC Continus 60mg tablets (Napp Pharmaceuticals Ltd)
8500	CODEINE PHOSPHATE/PARACETAMOL/SODIUM CIT 8 MG CAP
8732	BUCLIZINE HYD/CODEINE PHOS/DOCUSATE SOD/ 6.25 MG TAB
8822	Morphine 60mg modified-release tablets
8867	MORPHINE SULPHATE CR 30 MG TAB
8876	Oramorph 20mg/ml concentrated oral solution (Boehringer Ingelheim Ltd)
8959	MORPHINE SULPHATE 15 MG TAB
9001	Diconal tablets (Amdipharm Plc)
9044	Codis 500 dispersible tablets (Reckitt Benckiser Healthcare (UK) Ltd)

prodcode	Product name
9129	Paracetamol 250mg with aspirin 250mg & codeine 6.8mg tablet
9137	Morphine 20mg tablets
9163	Remedeine 20mg+500mg Effervescent tablet (Napp Pharmaceuticals Ltd)
9183	Morphine 100mg modified-release tablets
9209	DHC Continus 90mg tablets (Napp Pharmaceuticals Ltd)
9275	DHC Continus 120mg tablets (Napp Pharmaceuticals Ltd)
9313	Dihydrocodeine 90mg modified-release tablets
9325	Hydromorphone 4mg modified-release capsules
9330	Palladone 2.6mg capsules (Napp Pharmaceuticals Ltd)
9331	Palladone SR 4mg capsules (Napp Pharmaceuticals Ltd)
9332	Palladone SR 2mg capsules (Napp Pharmaceuticals Ltd)
9337	MXL 30mg capsules (Napp Pharmaceuticals Ltd)
9342	MXL 60mg capsules (Napp Pharmaceuticals Ltd)
9371	MXL 120mg capsules (Napp Pharmaceuticals Ltd)
9381	MXL 90mg capsules (Napp Pharmaceuticals Ltd)
9389	Zamadol SR 50mg capsules (Meda Pharmaceuticals Ltd)
9396	Zamadol SR 100mg capsules (Meda Pharmaceuticals Ltd)
9432	Aspirin 500mg / Codeine 8mg soluble tablets
9457	Paracetamol 500mg with codeine phosphate 8mg tablet
9460	Paracetamol 500mg with codeine phosphate 8mg capsule
9462	Paracetamol 500mg with codeine phosphate 8mg effervescent tablet
9484	Morphine sulphate 24 60mg Modified-release capsule
9516	Kapake 30mg/500mg capsules (Galen Ltd)
9557	Morphine 15mg modified-release tablets
9562	Remedeine 30mg+500mg Effervescent tablet (Napp Pharmaceuticals Ltd)
9602	Morphine 5mg modified-release tablets
9615	Palladone 1.3mg capsules (Napp Pharmaceuticals Ltd)
9672	Morphine 100mg modified-release granules sachets sugar free

prodcode	Product name
9739	Tramadol 100mg effervescent powder sachets sugar free
9742	Solpadeine Soluble tablet (GlaxoSmithKline Consumer Healthcare)
9785	Remedeine 30mg+500mg Tablet (Napp Pharmaceuticals Ltd)
9855	Paracetamol 500mg / Dihydrocodeine 20mg tablets
9874	OxyNorm liquid 5mg/5ml oral solution (Napp Pharmaceuticals Ltd)
9917	Kapake Insts 30mg/500mg effervescent powder sachets (Galen Ltd)
9927	OxyContin 40mg modified-release tablets (Napp Pharmaceuticals Ltd)
9960	Morphine sulphate 12 60mg Modified-release capsule
9973	OxyNorm 10mg capsules (Napp Pharmaceuticals Ltd)
10021	OxyContin 80mg modified-release tablets (Napp Pharmaceuticals Ltd)
10023	Dihydrocodeine with paracetamol 20mg+500mg tablets
10099	Paracetamol 500mg with codeine phosphate 8mg & buclizine 6.25mg
10122	Dihydrocodeine 10mg with paracetamol 500mg/5ml oral suspension sugar free
10176	Codipar 15mg/500mg tablets (AMCo)
10178	Solpadeine Plus capsules (Omega Pharma Ltd)
10196	Solpadeine Headache tablets (GlaxoSmithKline Consumer Healthcare)
10205	BuTrans 10micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
10226	Solpadeine Plus tablets (Omega Pharma Ltd)
10239	MXL 150mg capsules (Napp Pharmaceuticals Ltd)
10509	Fortagesic Tablet (Sanofi-Synthelabo Ltd)
10519	CODEINE PHOS/IBUPROFEN SR (20MG/300MG) TAB
10525	MST CONTINUS 30 MG SUS
10578	Palfium 10mg tablets (Roche Products Ltd)
10602	Paracodol 8mg/500mg effervescent tablets (Bayer Plc)
10740	DISTALGESIC SOLUBLE TAB
10769	Fortral 50mg Capsule (Sanofi-Synthelabo Ltd)
10829	MST CONTINUS 20 MG SUS
10907	MORPHINE SULPHATE CR 15 MG TAB

prodcode	Product name
10922	Durogesic 100micrograms transdermal patches (Janssen-Cilag Ltd)
11009	Paracetamol 500mg with codeine phosphate 8mg & caffeine 30mg tablet
11101	Zydol 50mg soluble tablets (Grunenthal Ltd)
11250	Migraleve - 2 8mg+500mg Tablet (Pfizer Consumer Healthcare Ltd)
11325	Paracetamol 500mg with codeine phosphate 30 mg tablet
11342	Oramorph 30mg/5ml oral solution unit dose vials (Boehringer Ingelheim Ltd)
11405	Oxycodone 10mg/ml oral solution sugar free
11461	Ibuprofen 300mg modified-release / Codeine 20mg tablets
11549	Tramadol 75mg modified-release tablets
11554	Ibuprofen 200mg / Codeine 12.8mg tablets
11559	Tramadol 50mg effervescent powder sachets sugar free
11584	Buprenorphine 70micrograms/hour transdermal patches
11665	Zapain 30mg/500mg tablets (AMCo)
11698	Morphine sulphate 24 30mg Modified-release capsule
11734	Tramadol 50mg orodispersible tablets sugar free
11746	Tramadol 300mg modified-release tablets
11748	Tramadol 400mg modified-release tablets
11755	Morcap SR 20mg capsules (Hospira UK Ltd)
11807	Paracetamol 500mg with codeine 12.8mg tablet
11838	Morphine 200mg modified-release tablets
11843	Fentanyl 200microgram lozenges
11945	Syndol Tablet (SSL International Plc)
11961	Veganin Tablet (Pfizer Consumer Healthcare Ltd)
11982	Durogesic DTrans 12micrograms transdermal patches (Janssen-Cilag Ltd)
12011	MORPHINE SULPHATE CR 60 MG TAB
12020	Dipipanone 10mg / Cyclizine 30mg tablets
12076	Dextropropoxyphene 60mg capsules
12508	MORPHINE SULPHATE CR 100 MG TAB

prodcode	Product name
12583	MORPHINE SULPHATE CR 5 MG TAB
12591	Morphine 60mg modified-release granules sachets sugar free
12604	MST Continus Suspension 100mg granules sachets (Napp Pharmaceuticals Ltd)
12608	MORPHINE SULPHATE CR 200 MG TAB
12709	Ibuprofen and codeine 200mg + 12.5mg Tablet
12889	Oramorph 100mg/5ml oral solution unit dose vials (Boehringer Ingelheim Ltd)
12900	MST Continus Suspension 30mg granules sachets (Napp Pharmaceuticals Ltd)
12992	Aspirin 500mg / Codeine 8mg dispersible tablets sugar free
13076	Actiq 200microgram lozenges with integral oromucosal applicator (Teva UK Ltd)
13114	Zomorph 10mg modified-release capsules (Archimedes Pharma UK Ltd)
13117	Zomorph 30mg modified-release capsules (Archimedes Pharma UK Ltd)
13300	BuTrans 20micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
13588	MORPHINE SULPHATE susp C/R 30 MG
13598	ASPIRIN & CODEINE 500 MG TAB
13711	Morcap sr 20mg Modified-release capsule (Faulding Pharmaceuticals (Dbl))
13813	Zamadol 50mg capsules (Meda Pharmaceuticals Ltd)
13893	Nurofen Plus tablets (Reckitt Benckiser Healthcare (UK) Ltd)
13995	Morphine sulphate 24 200mg Modified-release capsule
13997	Morphine sulphate 100mg Modified-release capsule
14050	Morphine sulphate 12 100mg Modified-release capsule
14063	Zomorph 100mg modified-release capsules (Archimedes Pharma UK Ltd)
14156	Morphine sulfate 30mg/5ml oral solution unit dose vials sugar free
14226	Morphine 30mg modified-release granules sachets sugar free
14378	Feminax tablets (Bayer Plc)
14394	Phenazocine hydrobromide 5mg tablet
14490	Tramake 50mg capsules (Galen Ltd)
14602	Co-codamol 60mg/1000mg effervescent powder sachets sugar free
14676	Paracetamol 500mg with codeine phosphate 8mg & caffeine 30mg effervescent tablet

prodcode	Product name
14688	Paracetamol 500mg with dihydrocodeine 10mg tablet
14785	Paracetamol500mg with codeine phosphate 15mg tablet
14900	Durogesic DTrans 100micrograms transdermal patches (Janssen-Cilag Ltd)
14912	Codeine phosphate 8mg with Paracetamol 500mg capsules
14964	Solpadeine Plus soluble tablets (Omega Pharma Ltd)
15064	MORPHINE HCL 10MG/CHLOROFORM WATER > 5ML SOL
15198	Co-dydramol 10mg+500mg Tablet (C P Pharmaceuticals Ltd)
15337	Fentanyl 1.2mg lozenges
15779	Codeine 8mg with aspirin 500mg soluble tablets
15781	Morphine sulphate 24 90mg Modified-release capsule
15792	Hydromorphone 2mg modified-release capsules
15798	Hydromorphone 8mg modified-release capsules
15815	Morphine 50mg tablets
15831	Codeine phosphate 30mg with paracetamol 500mg effervescent powder sugar free
15871	Kapake Insts 60mg/1000mg effervescent powder sachets (Galen Ltd)
15950	Zomorph 200mg modified-release capsules (Archimedes Pharma UK Ltd)
15964	Zomorph 60mg modified-release capsules (Archimedes Pharma UK Ltd)
16039	Solpadeine Capsule (GlaxoSmithKline Consumer Healthcare)
16076	Paracetamol 325mg with tramadol 37.5 mg tablet
16112	Paramol soluble tablets (SSL International Plc)
16271	Zydol XL 300mg tablets (Grunenthal Ltd)
16273	Oramorph sr 30mg Tablet (Boehringer Ingelheim Ltd)
16395	Zydol XL 200mg tablets (Grunenthal Ltd)
16467	Codeine phosphate 30mg with paracetamol 500mg effervescent tablets
16592	Parahypon Tablet (Wellcome Consumer)
16618	Tilofyl 75micrograms/hour transdermal patches (Tillomed Laboratories Ltd)
16818	Paracetamol 500mg with codeine phosphate 30mg effervescent powder sugar free
17158	Panadeine forte Tablet (Sanofi-Synthelabo Ltd)

prodcode	Product name
17167	Narphen 5mg Tablet (Smith & Nephew Healthcare Ltd)
17386	Pethidine 50mg Tablet (Roche Products Ltd)
17563	Solpadeine Max 12.8mg/500mg tablets (Omega Pharma Ltd)
17719	SOLPADOL
17808	CO-CODAMOL 30MG/500MG
17825	MORPHINE HCL 5MG/CHLOROFORM WATER TO 5ML SOL
17893	Oramorph sr 60mg Tablet (Boehringer Ingelheim Ltd)
17917	Dihydrocodeine with paracetamol 20mg with 500mg effervescent tablets
17926	Aspirin 400mg with Codeine 8mg tablets
17936	MXL 200mg capsules (Napp Pharmaceuticals Ltd)
17943	Sevredol 20mg/ml concentrated oral solution (Napp Pharmaceuticals Ltd)
17998	Medocodene 30mg/500mg capsules (UCB Pharma Ltd)
18166	Morphine sulphate 12 200mg Modified-release capsule
18174	Actiq 400microgram lozenges with integral oromucosal applicator (Teva UK Ltd)
18221	Codeine phosphate 15mg with paracetamol 500mg tablets
18261	Aspirin 500mg with Papaveretum 7.71mg dispersible tablets
18482	Paracetamol 325mg with dextropropoxyphene 32.5mg tablet
18626	MORPHINE SULPHATE 200 MG TAB
18639	MORPHINE SULPHATE SR 100 MG TAB
18656	SRM-RHOTARD 10mg Modified-release tablet (Pharmacia Ltd)
18700	SRM-RHOTARD 30mg Modified-release tablet (Pharmacia Ltd)
18734	Oramorph sr 100mg Tablet (Boehringer Ingelheim Ltd)
18801	Morcap SR 100mg capsules (Hospira UK Ltd)
18881	Morphgesic SR 10mg tablets (AMCo)
18922	Solpadeine Headache soluble tablets (Omega Pharma Ltd)
19069	Dextropropoxyphene 60mg capsules
19092	Morcap sr 50mg Modified-release capsule (Faulding Pharmaceuticals (Dbl))
19206	Paracetamol 500mg / Dihydrocodeine 7.46mg tablets

prodcode	Product name
19291	Morphine sulfate 100mg/5ml oral solution unit dose vials sugar free
19317	Omnopon 10mg Tablet (Roche Products Ltd)
19449	Morphgesic SR 30mg tablets (AMCo)
19471	Morphgesic SR 60mg tablets (AMCo)
19477	Morphgesic SR 100mg tablets (AMCo)
19550	CO-PROXAMOL
19724	ASPIRIN & CODEINE paed 75 MG TAB
19764	Papaveretum 10mg tablet
19854	Propain plus Tablet (Ceuta Healthcare Ltd)
19954	Palladone SR 16mg capsules (Napp Pharmaceuticals Ltd)
19972	Hydromorphone 16mg modified-release capsules
19993	Dromadol SR 100mg tablets (Teva UK Ltd)
20008	MORPHINE SULPHATE 20 MG CAP
20077	Paracetamol 400mg with codeine phosphate 10mg with diphenhydramine 5mg & caffeine 50mg tablet
20127	Codeine phosphate 8mg with aspirin 400mg with caffeine dispersible tablets
20219	MORPHINE SULPHATE 120 MG CAP
20256	Paracetamol 450mg with codeine phosphate 10mg with doxylamine 5mg & caffeine 30mg tablet
20310	Zamadol Melt 50mg tablets (Meda Pharmaceuticals Ltd)
20565	Paracetamol 500mg with codeine phosphate 8mg & caffeine 30mg capsule
20853	Propain Tablet (Sankyo Pharma UK Ltd)
21067	Doloxene Capsule (Eli Lilly and Company Ltd)
21104	PARACETAMOL/CODEINE PHOSPHATE 500 MG TAB
21113	Dihydrocodeine with paracetamol forte 30mg with 500mg effervescent tablets
21229	Paracetamol 500mg / Dihydrocodeine 7.46mg effervescent tablets sugar free
21251	Ultramol Soluble tablets (Zentiva)
21256	Tramake Insts 50mg sachets (Galen Ltd)
21275	Palladone SR 8mg capsules (Napp Pharmaceuticals Ltd)

prodcode	Product name
21285	Palladone SR 24mg capsules (Napp Pharmaceuticals Ltd)
21397	Zydol XL 400mg tablets (Grunenthal Ltd)
21673	Paracetamol 500mg with codeine phosphate 8mg & caffeine 30mg effervescent tablet
21703	Paracetamol 1000mg with codeine phosphate 60mg effervescent powder sugar free
21746	Pharmidone Tablet (Pharmacia Ltd)
21777	Dromadol SR 200mg tablets (Teva UK Ltd)
21797	Zamadol SR 200mg capsules (Meda Pharmaceuticals Ltd)
21880	Zapain 30mg/500mg capsules (AMCo)
21927	CO-DYDRAMOL
21947	Zydol XL 150mg tablets (Grunenthal Ltd)
22024	Rhotard Morphine SR 10mg tablets (Sovereign Medical Ltd)
22026	Rhotard Morphine SR 30mg tablets (Sovereign Medical Ltd)
22066	Tilofyl 50micrograms/hour transdermal patches (Tillomed Laboratories Ltd)
22450	ASPIRIN & CODEINE 75 MG TAB
22627	CODEINE PHOSPHATE 15/PARACETAMOL 500MG TAB
22690	Morphine sulphate 24 120mg Modified-release capsule
22756	Filnarine SR 30mg tablets (Teva UK Ltd)
22764	Panadeine Tablet (GlaxoSmithKline UK Ltd)
22817	CO-CODAMOL SF EFF POWDER
23060	MST Continus Suspension 200mg granules sachets (Napp Pharmaceuticals Ltd)
23420	Codeine phosphate 60mg with paracetamol 1000mg effervescent powder sugar free
23496	CO-CODAPRIN DISPERSIBLE
23625	Dromadol SR 150mg tablets (Teva UK Ltd)
23952	Panadeine Effervescent tablet (Sanofi-Synthelabo Ltd)
23981	Zamadol SR 150mg capsules (Meda Pharmaceuticals Ltd)
24192	TEMGESIC
24209	CO-CODAMOL EFFERVESCENT
24383	Tramake Insts 100mg sachets (Galen Ltd)

prodcode	Product name
24414	TEMGESIC
24453	Morcap sr 100mg Modified-release capsule (Faulding Pharmaceuticals (Dbl))
24498	ASPIRIN/CODEINE PHOSPHATE/PARACETAMOL 300 MG TAB
24733	DEXTROPROPOXYPHENE HCl S/R 150 MG CAP
24736	Hydromorphone 24mg modified-release capsules
24828	Hypon Tablet (Wellcome Medical Division)
24859	CODEINE 8MG & PARACETAMOL 500MG SUP
24986	Fentanyl 1.6mg lozenges
24996	Codeine phosphate 8mg with paracetamol 500mg with buclizine 6.25mg tablets
25109	Veganin tablets (Omega Pharma Ltd)
25199	Actiq 600microgram lozenges with integral oromucosal applicator (Teva UK Ltd)
25330	Solpaflex tablets (GlaxoSmithKline Consumer Healthcare)
25514	Paracetamol 500mg with codeine phosphate 10mg tablet
25529	Paracetamol 500mg with codeine phosphate 8mg & caffeine 30mg tablet
25959	ASPIRIN/CAFFEINE/DEXTROPROPOXYPHENE NAPS PUL
25979	Doloxene 60mg Capsule (Eli Lilly and Company Ltd)
26021	Actiq 1.6mg lozenges with integral oromucosal applicator (Teva UK Ltd)
26283	Filnarine SR 10mg tablets (Teva UK Ltd)
26284	Filnarine SR 100mg tablets (Teva UK Ltd)
26336	Dromadol XL 300mg tablets (IVAX Pharmaceuticals UK Ltd)
26653	DIHYDROCODEINE 10mg/PARACETAMOL 500mg
26908	Actiq 800microgram lozenges with integral oromucosal applicator (Teva UK Ltd)
26986	Zamadol 24hr 200mg modified-release tablets (Meda Pharmaceuticals Ltd)
27058	Filnarine SR 60mg tablets (Teva UK Ltd)
27353	CAFFEINE /CODEINE PHOS./DOXYLAMINE SUCCI 30 MG TAB
27436	MORPHINE SULPHATE 90 MG CAP
27548	OXYCODONE
27591	Zamadol 24hr 150mg modified-release tablets (Meda Pharmaceuticals Ltd)

prodcode	Product name
27598	CAFFEINE/CODEINE PHOS./DIPHENHYDRAMINE H 50 MG TAB
27749	Morphine sulphate 24 150mg Modified-release capsule
27784	Co-codamol 8mg/500mg tablets (Actavis UK Ltd)
27785	Co-codamol 30mg/500mg tablets (Zentiva)
28189	Tilofyl 100micrograms/hour transdermal patches (Tillomed Laboratories Ltd)
28253	Co-proxamol 32.5/325 Oral suspension (Rosemont Pharmaceuticals Ltd)
28503	MORPHINE SULPHATE 100 MG CAP
28598	Paracetamol with dihydrocodeine 500mg +10mg/5ml suspension sugar free
28606	ASPIRIN/CAFFEINE/CODEINE PHOSPHATE 300 MG TAB
28728	Zamadol 24hr 300mg modified-release tablets (Meda Pharmaceuticals Ltd)
28780	Co-dydramol 10mg/500mg tablets (A A H Pharmaceuticals Ltd)
28784	Codeine phosphate 8mg with aspirin 400mg tablets
28837	MORPHINE SULPHATE 200 MG CAP
29020	Morphine 200mg modified-release granules sachets sugar free
29324	Dromadol SR 75mg tablets (IVAX Pharmaceuticals UK Ltd)
29342	Co-codamol 8mg+500mg Tablet (M & A Pharmachem Ltd)
29373	Pardale 400mg+9mg+10mg Tablet (Martindale Pharmaceuticals Ltd)
29488	Co-codamol 8mg/500mg effervescent tablets (Zentiva)
29577	Actiq 1.2mg lozenges with integral oromucosal applicator (Teva UK Ltd)
29828	ACETYLSALICYLIC ACID / CODEINE PHOSPHATE MG TAB
29860	Tramadol 50mg capsules (IVAX Pharmaceuticals UK Ltd)
30021	Paracetamol 500mg with codeine phosphate 13.5mg tablet
30123	Panadol Ultra 12.8mg/500mg tablets (GlaxoSmithKline Consumer Healthcare)
30165	Co-dydramol (dihydrocodeine and paracetamol) 7.46mg with 500mg tablets
30295	Dihydrocodeine with paracetamol 7.46mg+500mg tablets
30444	Co-dydramol 10mg/500mg tablets (Generics (UK) Ltd)
30556	Co-codamol 8mg/500mg effervescent tablets (Fannin UK Ltd)
30954	Co-proxamol 32.5mg/325mg tablets (Actavis UK Ltd)

prodcode	Product name
30966	Co-proxamol 32.5/325 Tablet (Dista Products Ltd)
31053	Tilofyl 25micrograms/hour transdermal patches (Tillomed Laboratories Ltd)
31105	Dromadol XL 200mg tablets (IVAX Pharmaceuticals UK Ltd)
31107	Dromadol XL 150mg tablets (IVAX Pharmaceuticals UK Ltd)
31155	Parake Tablet (Galen Ltd)
31452	Codeine 30mg tablets (Wockhardt UK Ltd)
31498	ASPIRIN / CAFFEINE CIT./ CODEINE PHOS./ 200 MG TAB
31577	Co-codamol 30mg/500mg capsules (A A H Pharmaceuticals Ltd)
31700	Codeine 15mg tablets (Actavis UK Ltd)
31734	Dromadol XL 400mg tablets (IVAX Pharmaceuticals UK Ltd)
31871	Paracetamol 450mg with codeine phosphate 8.1mg tablet
31894	Safapryn -Co Tablet (Pfizer Ltd)
31935	Pethidine 50mg Tablet (Roche Products Ltd)
31943	Codeine 30mg tablets (IVAX Pharmaceuticals UK Ltd)
32165	Tramadol 50mg Capsule (Generics (UK) Ltd)
32450	Zamadol 24hr 400mg modified-release tablets (Meda Pharmaceuticals Ltd)
32459	MORPHINE SULPHATE 50 MG CAP
32460	MORPHINE SULPHATE 150 MG CAP
32519	Painex caplets (Sandoz Ltd)
32668	KAPAKE INSTS
32692	Co-codamol 8mg/500mg effervescent tablets (A A H Pharmaceuticals Ltd)
32891	Syndol caplets (Sanofi)
32926	Co-dydramol 10mg/500mg tablets (Actavis UK Ltd)
33260	Paracetamol with codeine with hyoscine & caffeine tablet
33340	Co-dydramol 10mg+500mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)
33495	BUCLIZINE HYD/CODEINE PHOS/PARACET / COD 6.25 MG TAB
33643	Co-codamol 8mg+500mg Tablet (Family Health)
33647	Co-proxamol 32.5mg/325mg tablets (A A H Pharmaceuticals Ltd)

prodcode	Product name
33653	Co-codamol 8mg/500mg tablets (IVAX Pharmaceuticals UK Ltd)
33654	Dihydrocodeine 30mg tablets (Wockhardt UK Ltd)
33679	Co-codamol 8mg/500mg tablets (Zentiva)
33688	Co-codamol 30mg/500mg effervescent tablets (Fannin UK Ltd)
33743	Dihydrocodeine with paracetamol 7.46mg with 500mg effervescent tablets
33961	Co-codamol 30mg/500mg capsules (IVAX Pharmaceuticals UK Ltd)
33995	Co-proxamol 32.5/325 Tablet (Berk Pharmaceuticals Ltd)
34008	Dihydrocodeine 30mg tablets (IVAX Pharmaceuticals UK Ltd)
34022	Co-proxamol 32.5mg/325mg tablets (Teva UK Ltd)
34065	Tramadol sr 150mg Modified-release tablet (Winthrop Pharmaceuticals Ltd)
34229	Co-codamol 8mg+500mg Dispersible tablet (Rhone-Poulenc Rorer Ltd)
34257	Co-codamol 8mg/500mg effervescent tablets (Generics (UK) Ltd)
34260	Tramadol sr 100mg Modified-release tablet (Winthrop Pharmaceuticals Ltd)
34264	Co-codamol 30mg/500mg tablets (IVAX Pharmaceuticals UK Ltd)
34281	Tramadol sr 200mg Modified-release tablet (Winthrop Pharmaceuticals Ltd)
34319	Co-proxamol 32.5mg/325mg tablets (Zentiva)
34348	Codeine 15mg tablets (A A H Pharmaceuticals Ltd)
34349	Co-proxamol 32.5mg/325mg tablets (IVAX Pharmaceuticals UK Ltd)
34383	Codeine 30mg tablets (A A H Pharmaceuticals Ltd)
34397	Co-proxamol 32.5mg+325mg Tablet (M & A Pharmachem Ltd)
34422	Tramadol 50mg capsules (Actavis UK Ltd)
34440	Dihydrocodeine 30mg tablets (A A H Pharmaceuticals Ltd)
34444	Codeine 15mg tablets (Wockhardt UK Ltd)
34468	Co-proxamol 32.5mg/325mg tablets (Sandoz Ltd)
34477	Morphine sulfate 10mg/5ml oral solution (Martindale Pharmaceuticals Ltd)
34495	Co-codamol 8mg/500mg tablets (Generics (UK) Ltd)
34497	Co-codamol 8mg+500mg Tablet (Berk Pharmaceuticals Ltd)
34518	Co-codamol 8mg/500mg tablets (A A H Pharmaceuticals Ltd)

prodcode	Product name
34521	Tramadol 50mg capsules (A A H Pharmaceuticals Ltd)
34546	Co-proxamol 32.5mg+325mg Tablet (Neo Laboratories Ltd)
34552	Codeine 30mg tablets (Actavis UK Ltd)
34554	Co-proxamol 32.5/325 Tablet (C P Pharmaceuticals Ltd)
34570	Tramadol 50mg capsules (Teva UK Ltd)
34579	Dihydrocodeine 30mg tablets (Actavis UK Ltd)
34597	Co-proxamol 32.5mg/325mg tablets (Kent Pharmaceuticals Ltd)
34639	Tramadol 50mg capsules (Genus Pharmaceuticals Ltd)
34662	Dihydrocodeine 30mg tablets (Generics (UK) Ltd)
34667	Co-codamol 30mg/500mg tablets (A A H Pharmaceuticals Ltd)
34730	Dihydrocodeine 30mg Tablet (Berk Pharmaceuticals Ltd)
34737	Co-dydramol 10mg/500mg tablets (Teva UK Ltd)
34784	Co-codamol 8mg/500mg effervescent tablets (Sandoz Ltd)
34789	Codeine 30mg tablets (Kent Pharmaceuticals Ltd)
34808	Tramadol 50mg capsules (PLIVA Pharma Ltd)
34815	Co-codamol 8mg/500mg tablets (Kent Pharmaceuticals Ltd)
34840	Co-codamol 30mg/500mg tablets (Almus Pharmaceuticals Ltd)
34845	Co-codamol 30mg/500mg effervescent tablets (Zentiva)
34865	Co-codamol 8mg+500mg Tablet (C P Pharmaceuticals Ltd)
34920	Co-dydramol 10mg+500mg Tablet (Berk Pharmaceuticals Ltd)
34939	Co-dydramol 10mg+500mg Tablet (Duncan Flockhart Ltd)
34968	Co-codamol 8mg/500mg tablets (Teva UK Ltd)
35347	Tramadol 24 Modified-release tablet
35438	Tramquel SR 100mg capsules (Beechmere Pharmaceuticals Ltd)
35651	Tradorec XL 200mg tablets (Paladin Labs Europe Ltd)
35656	Tradorec XL 100mg tablets (Paladin Labs Europe Ltd)
35792	Codeine 25mg/5ml oral solution (Thornton & Ross Ltd)
35806	Larapam SR 100mg tablets (Sandoz Ltd)

prodcode	Product name
35965	Medocodene 30mg/500mg effervescent tablets (Generics (UK) Ltd)
35968	Matrifen 25micrograms/hour transdermal patches (Teva UK Ltd)
36019	Co-dydramol 10mg+500mg Tablet (M & A Pharmachem Ltd)
36035	Tradorec XL 300mg tablets (Paladin Labs Europe Ltd)
36040	Matrifen 100micrograms/hour transdermal patches (Teva UK Ltd)
36152	Propain caplets (Ceuta Healthcare Ltd)
36211	Matrifen 50micrograms/hour transdermal patches (Teva UK Ltd)
36472	Paracetamol 500 mg+ pentazocine 15mg tablet
36488	Co-codamol 30mg/500mg capsules (Generics (UK) Ltd)
36608	Co-codamol Effervescent tablet (A A H Pharmaceuticals Ltd)
36697	Mabron 200mg modified-release tablets (Morningside Healthcare Ltd)
36732	Tramadol 50mg modified-release tablets
36873	Zydol SR 50mg tablets (Grunenthal Ltd)
36949	Tramquel SR 50mg capsules (Beechmere Pharmaceuticals Ltd)
36993	Co-codamol 30mg/500mg capsules (Teva UK Ltd)
37020	Tramadol 150mg modified-release tablets
37021	Tramadol 200mg modified-release tablets
37291	Co-dydramol 10mg/500mg tablets (Ranbaxy (UK) Ltd)
37298	PARACETAMOL,CAFFEINE,CODEINE & NICOTINAM TAB
37348	Codeine phosphate with paracetamol, doxylamine and caffeine 10mg with 450mg with 5mg with 30mg tablets
37719	Fentalis Reservoir 100micrograms/hour transdermal patches (Sandoz Ltd)
37779	Fentalis Reservoir 25micrograms/hour transdermal patches (Sandoz Ltd)
37816	Cuprofen PLUS tablets (SSL International Plc)
37831	Mabron 100mg modified-release tablets (Morningside Healthcare Ltd)
37867	Tramadol (roi) Tablet
37904	Co-codamol 12.8mg/500mg tablets
37923	Fentalis Reservoir 50micrograms/hour transdermal patches (Sandoz Ltd)

prodcode	Product name
37928	Matrifen 12micrograms/hour transdermal patches (Teva UK Ltd)
37954	Mezolar Matrix 12micrograms/hour transdermal patches (Sandoz Ltd)
37960	Osmach 50micrograms/hour transdermal patches (Teva UK Ltd)
37968	Fentanyl 40micrograms/dose transdermal system
38013	Pethidine 50mg capsules
38031	Mezolar Matrix 25micrograms/hour transdermal patches (Sandoz Ltd)
38085	Paracetamol 500mg with codeine phosphate 10mg capsule
38088	Paracetamol 500mg with codeine phosphate 30 mg tablet
38103	Pethidine 25mg Tablet (Roche Products Ltd)
38196	Larapam SR 200mg tablets (Sandoz Ltd)
38301	Cyclizine 30mg with dipipanone 10mg tablets
38326	Mezolar Matrix 75micrograms/hour transdermal patches (Sandoz Ltd)
38351	Matrifen 75micrograms/hour transdermal patches (Teva UK Ltd)
38363	Codeine phosphate 12.8mg with paracetamol 500mg tablets
38365	Fentalis Reservoir 75micrograms/hour transdermal patches (Sandoz Ltd)
38430	Co-dydramol 10mg+500mg Tablet (Merck Generics (UK) Ltd)
38521	Dihydrocodeine 30mg tablets (Teva UK Ltd)
38528	Tramadol 50mg Capsule (Tillomed Laboratories Ltd)
38553	Mezolar Matrix 100micrograms/hour transdermal patches (Sandoz Ltd)
38950	Remedeine Forte tablets (Crescent Pharma Ltd)
38956	Tramquel SR 200mg capsules (Beechmere Pharmaceuticals Ltd)
38970	DF 118 Forte 40mg tablets (Martindale Pharmaceuticals Ltd)
39084	Osmach 100micrograms/hour transdermal patches (Ratiopharm UK Ltd)
39180	Mezolar Matrix 50micrograms/hour transdermal patches (Sandoz Ltd)
39251	Osmach 25micrograms/hour transdermal patches (Teva UK Ltd)
39340	Co-codamol 8mg/500mg caplets (Vantage)
39419	Palfium 5mg Tablet (IDIS World Medicines)
39461	Solpadeine Migraine Ibuprofen & Codeine tablets (Omega Pharma Ltd)

prodcode	Product name
39469	Fentanyl 100microgram sublingual tablets sugar free
39475	Oxycodone 10mg / Naloxone 5mg modified-release tablets
39477	Targinact 10mg/5mg modified-release tablets (Napp Pharmaceuticals Ltd)
39478	Targinact 20mg/10mg modified-release tablets (Napp Pharmaceuticals Ltd)
39498	Oxycodone 20mg / Naloxone 10mg modified-release tablets
39505	Marol 100mg modified-release tablets (Morningside Healthcare Ltd)
39518	Abstral 100microgram sublingual tablets (ProStrakan Ltd)
39558	Dihydrocodeine 30mg tablets (Zentiva)
39590	Fentanyl 200microgram sublingual tablets sugar free
39709	Marol 200mg modified-release tablets (Morningside Healthcare Ltd)
39723	Fentanyl 100microgram buccal tablets sugar free
39746	Effentora 100microgram buccal tablets (Teva UK Ltd)
39750	Marol 150mg modified-release tablets (Morningside Healthcare Ltd)
39756	Abstral 200microgram sublingual tablets (ProStrakan Ltd)
39798	Nobligan retard 100mg tablets (Grunenthal Ltd)
39799	Abstral 800microgram sublingual tablets (ProStrakan Ltd)
39811	Maxitram SR 200mg capsules (Chiesi Ltd)
39842	Meptid 200mg tablets (Almirall Ltd)
39929	Effentora 200microgram buccal tablets (Teva UK Ltd)
39987	Abstral 400microgram sublingual tablets (ProStrakan Ltd)
40018	Fentanyl 200microgram buccal tablets sugar free
40058	Tramulief SR 100mg tablets (AMCo)
40060	Tramulief SR 200mg tablets (AMCo)
40061	Tramulief SR 150mg tablets (AMCo)
40098	Fentanyl 400microgram sublingual tablets sugar free
40128	Effentora 400microgram buccal tablets (Teva UK Ltd)
40159	Dihydrocodeine 10mg/5ml oral solution (Martindale Pharmaceuticals Ltd)
40166	Tramadol 50mg capsules (Niche Generics Ltd)

prodcode	Product name
40239	Pethidine 50mg tablets (Martindale Pharmaceuticals Ltd)
40249	Maxitram SR 100mg capsules (Chiesi Ltd)
40254	Maxitram SR 50mg capsules (Chiesi Ltd)
40385	Co-codamol 8mg/500mg effervescent tablets (Almus Pharmaceuticals Ltd)
40422	Co-dydramol 10mg/500mg tablets (Zentiva)
40434	Effentora 600microgram buccal tablets (Teva UK Ltd)
40508	Abstral 600microgram sublingual tablets (ProStrakan Ltd)
40563	Morphine 30mg modified-release capsules
40576	Fentanyl 400microgram buccal tablets sugar free
40616	Oxycodone 5mg / Naloxone 2.5mg modified-release tablets
40645	Targinact 5mg/2.5mg modified-release tablets (Napp Pharmaceuticals Ltd)
40662	Co-codamol 8mg/500mg effervescent tablets (Actavis UK Ltd)
40663	Co-codamol 30mg/500mg effervescent tablets (Actavis UK Ltd)
40718	Tramadol 50mg capsules (Almus Pharmaceuticals Ltd)
40785	Oxycodone 40mg / Naloxone 20mg modified-release tablets
40805	Tramquel SR 150mg capsules (Beechmere Pharmaceuticals Ltd)
40883	Maxitram SR 150mg capsules (Chiesi Ltd)
40926	Larapam SR 150mg tablets (Sandoz Ltd)
40940	Fentanyl 300microgram sublingual tablets sugar free
40957	Effentora 800microgram buccal tablets (Teva UK Ltd)
40961	Targinact 40mg/20mg modified-release tablets (Napp Pharmaceuticals Ltd)
41135	Fentanyl 50micrograms/dose nasal spray
41161	Osmach 75micrograms/hour transdermal patches (Teva UK Ltd)
41259	Co-codamol 30mg/500mg effervescent tablets (Teva UK Ltd)
41275	Co-codamol 8mg+500mg Tablet (Nucare Plc)
41276	Co-codamol 8mg/500mg tablets (Almus Pharmaceuticals Ltd)
41278	Co-dydramol 10mg/500mg tablets (IVAX Pharmaceuticals UK Ltd)
41286	Abstral 300microgram sublingual tablets (ProStrakan Ltd)

prodcode	Product name
41348	Fentanyl 600microgram sublingual tablets sugar free
41407	Co-proxamol 32.5mg/325mg tablets (Ranbaxy (UK) Ltd)
41416	Codeine 60mg tablets (Wockhardt UK Ltd)
41535	Codeine 30mg tablets (Teva UK Ltd)
41599	Codeine 15mg tablets (Teva UK Ltd)
41682	Co-codamol 30mg+500mg Effervescent tablet (Roche Consumer Health)
41976	Tramadol 100mg modified-release tablets (A A H Pharmaceuticals Ltd)
42021	Victanyl 100micrograms/hour transdermal patches (Actavis UK Ltd)
42208	Df118 30mg Tablet (Martindale Pharmaceuticals Ltd)
42213	Co-codamol 8mg/500mg capsules (Actavis UK Ltd)
42218	Co-codaprin 8mg/400mg dispersible tablets (A A H Pharmaceuticals Ltd)
42280	Tramadol 37.5mg / Paracetamol 325mg effervescent tablets sugar free
42332	Tramacet 37.5mg/325mg effervescent tablets (Grunenthal Ltd)
42380	Morphine sulphate 10mg Modified-release capsule
42399	Fentanyl 800microgram sublingual tablets sugar free
42538	Fentanyl 600microgram buccal tablets sugar free
42576	Victanyl 75micrograms/hour transdermal patches (Actavis UK Ltd)
42590	Osmanil 75micrograms/hour transdermal patches (Zentiva)
42591	Osmanil 25micrograms/hour transdermal patches (Zentiva)
42706	Feminax Period Pain capsules (Bayer Plc)
42791	Co-codamol 30mg/500mg tablets (Sandoz Ltd)
42798	Tramadol 150mg modified-release tablets (A A H Pharmaceuticals Ltd)
43089	Instanyl 100micrograms/dose nasal spray (Takeda UK Ltd)
43152	Osmanil 50micrograms/hour transdermal patches (Zentiva)
43198	Tramadol sr 50mg Capsule (Hillcross Pharmaceuticals Ltd)
43238	Co-codamol 30mg/500mg effervescent tablets (Generics (UK) Ltd)
43244	Co-codamol 30mg+500mg Effervescent tablet (Hillcross Pharmaceuticals Ltd)
43414	Co-codamol 8mg/500mg effervescent tablets (Bayer Plc)

prodcode	Product name
43441	Co-dydramol 10mg+500mg Tablet (Celltech Pharma Europe Ltd)
43504	Codeine phosphate Oral solution (William Ransom)
43513	Tramadol 50mg capsules (Zentiva)
43536	Co-proxamol 32.5/325 Tablet (Numark Management Ltd)
43550	Codeine 15mg tablets (Ranbaxy (UK) Ltd)
43617	Instanyl 200micrograms/dose nasal spray (Takeda UK Ltd)
43652	Morphine 100mg modified-release capsules
43657	Morphine 200mg modified-release capsules
43891	Co-proxamol 32.5mg/325mg/5ml oral suspension
44159	Solpadeine Max soluble tablets (Omega Pharma Ltd)
44210	Kapake 15mg/500mg tablets (Galen Ltd)
44311	DEXTROPROPOXYPHENE NAPSYLATE/ASPIRIN 100 MG TAB
44371	Mabron 150mg modified-release tablets (Morningside Healthcare Ltd)
44487	Osmanil 12micrograms/hour transdermal patches (Zentiva)
44837	Victanyl 50micrograms/hour transdermal patches (Actavis UK Ltd)
44924	Co-codamol 30mg/500mg tablets (Teva UK Ltd)
45092	Fentanyl 200micrograms/dose nasal spray
45231	Co-proxamol 32.5mg+325mg Tablet (Regent Laboratories Ltd)
45276	Co-proxamol 32.5mg+325mg Tablet (Sigma Pharmaceuticals Plc)
45439	PecFent 100micrograms/dose nasal spray (Archimedes Pharma UK Ltd)
45460	Osmanil 100micrograms/hour transdermal patches (Zentiva)
45549	Victanyl 25micrograms/hour transdermal patches (Actavis UK Ltd)
45598	Instanyl 50micrograms/dose nasal spray (Takeda UK Ltd)
45736	Morphine 60mg modified-release capsules
45745	OxyContin 30mg modified-release tablets (Napp Pharmaceuticals Ltd)
45766	OxyContin 60mg modified-release tablets (Napp Pharmaceuticals Ltd)
45788	OxyContin 15mg modified-release tablets (Napp Pharmaceuticals Ltd)
45790	Oxycodone 15mg modified-release tablets

prodcode	Product name
45800	Tapentadol 200mg modified-release tablets
45811	Tapentadol 50mg tablets
45827	Oxycodone 30mg modified-release tablets
45830	OxyContin 120mg modified-release tablets (Napp Pharmaceuticals Ltd)
45894	Fentanyl 100micrograms/dose nasal spray
45929	Oxycodone 60mg modified-release tablets
45936	Palexia 50mg tablets (Grunenthal Ltd)
45982	Palexia SR 50mg tablets (Grunenthal Ltd)
46018	Tapentadol 100mg modified-release tablets
46019	Tapentadol 150mg modified-release tablets
46020	Palexia SR 100mg tablets (Grunenthal Ltd)
46021	Tapentadol 50mg modified-release tablets
46022	Palexia 75mg tablets (Grunenthal Ltd)
46159	Palexia SR 150mg tablets (Grunenthal Ltd)
46187	Oxycodone 120mg modified-release tablets
46279	Tramadol 200mg modified-release capsules (A A H Pharmaceuticals Ltd)
46354	PecFent 400micrograms/dose nasal spray (Archimedes Pharma UK Ltd)
46461	Tapentadol 75mg tablets
46511	Co-codamol 15mg/500mg effervescent tablets sugar free
46555	Fentanyl 800microgram buccal tablets sugar free
46559	Fencino 12micrograms/hour transdermal patches (DB Ashbourne Ltd)
46560	Fencino 50micrograms/hour transdermal patches (DB Ashbourne Ltd)
46587	Tramadol 100mg/ml oral drops
46633	Co-codamol 8mg/500mg capsules (A A H Pharmaceuticals Ltd)
46643	Zeridame SR 150mg tablets (Actavis UK Ltd)
46657	Fencino 75micrograms/hour transdermal patches (DB Ashbourne Ltd)
46658	Fencino 100micrograms/hour transdermal patches (DB Ashbourne Ltd)
46659	Palexia SR 200mg tablets (Grunenthal Ltd)

prodcode	Product name
46729	Co-codamol 15mg/500mg capsules
46733	Fencino 25micrograms/hour transdermal patches (DB Ashbourne Ltd)
46898	Codipar 15mg/500mg capsules (AMCo)
46906	Co-codamol 8mg+500mg Effervescent tablet (Numark Management Ltd)
46925	Co-codaprin 8mg/400mg dispersible tablets (Actavis UK Ltd)
46987	Co-codamol 15mg+500mg Tablet (Hillcross Pharmaceuticals Ltd)
47003	Codeine 60mg tablets (Ranbaxy (UK) Ltd)
47071	Co-dydramol (dihydrocodeine and paracetamol) 10mg with 500mg/5ml oral suspension
47081	Paracetamol 500mg with codeine phosphate 12.8mg & caffeine 30mg effervescent tablet
47154	Filnarine SR 200mg tablets (Teva UK Ltd)
47200	Propain Plus caplets (Ceuta Healthcare Ltd)
47399	Tapentadol 250mg modified-release tablets
47413	Fentanyl 75micrograms/hr Transdermal patch (Sandoz Ltd)
47460	Palexia SR 250mg tablets (Grunenthal Ltd)
47508	Codipar 15mg/500mg effervescent tablets (AMCo)
47753	Morphine 90mg modified-release capsules
47759	Fentanyl 400micrograms/dose nasal spray
47847	Co-codamol 30mg/500mg capsules (Zentiva)
47854	Tramadol (roi) Tablet
47867	Morphine 150mg modified-release capsules
47919	Codeine phosphate 15mg Tablet (Wockhardt UK Ltd)
47949	Morphine 120mg modified-release capsules
47952	Codeine phosphate 30mg Tablet (Wockhardt UK Ltd)
47985	M-eslon 10mg Capsule (Trinity Pharmaceuticals Ltd)
48004	Codeine 30mg tablets (Ranbaxy (UK) Ltd)
48066	Codeine phosphate oral solution
48090	Tramadol 200mg modified-release tablets (A A H Pharmaceuticals Ltd)
48133	Dihydrocodeine 30mg tablets (Almus Pharmaceuticals Ltd)

prodcode	Product name
48136	Codeine 15mg tablets (Almus Pharmaceuticals Ltd)
48153	Codeine 60mg tablets (Actavis UK Ltd)
48311	Co-codamol 30mg/500mg caplets (Kent Pharmaceuticals Ltd)
48571	Durogesic DTrans 50micrograms transdermal patches (Waymade Healthcare Plc)
48775	Co-codamol 30mg/500mg caplets (AMCo)
49323	Marol 150mg modified-release tablets (Teva UK Ltd)
49324	Marol 100mg modified-release tablets (Teva UK Ltd)
49742	OxyContin 5mg modified-release tablets (DE Pharmaceuticals)
49787	OxyContin 20mg modified-release tablets (Lexon (UK) Ltd)
49940	OxyNorm 5mg capsules (Lexon (UK) Ltd)
50095	OxyNorm 5mg capsules (DE Pharmaceuticals)
50421	Codeine phosphate 15mg Tablet (Celltech Pharma Europe Ltd)
50468	Codeine 15mg tablets (Alliance Healthcare (Distribution) Ltd)
50532	Dihydrocodeine 30mg tablets (Bristol Laboratories Ltd)
50659	Codeine 60mg tablets (A A H Pharmaceuticals Ltd)
50671	Fentanyl 12micrograms/hour transdermal patches (A A H Pharmaceuticals Ltd)
50733	OxyContin 10mg modified-release tablets (Mawdsley-Brooks & Company Ltd)
50862	Marol 200mg modified-release tablets (Teva UK Ltd)
50929	Durogesic DTrans 12micrograms transdermal patches (Mawdsley-Brooks & Company Ltd)
50947	Tramadol 100mg modified-release capsules (Alliance Healthcare (Distribution) Ltd)
51084	Co-codamol 30mg/500mg capsules (AMCo)
51235	Fentanyl 25micrograms/hour transdermal patches (Phoenix Healthcare Distribution Ltd)
51327	Codeine 30mg tablets (Alliance Healthcare (Distribution) Ltd)
51381	Generic Solpadeine Plus capsules
51384	OxyNorm 20mg capsules (DE Pharmaceuticals)
51644	Codeine 30mg tablets (Bristol Laboratories Ltd)
51789	OxyNorm 10mg capsules (Waymade Healthcare Plc)

prodcode	Product name
51819	Co-codamol 8mg/500mg capsules (Phoenix Healthcare Distribution Ltd)
51896	OxyContin 80mg modified-release tablets (Mawdsley-Brooks & Company Ltd)
51937	Codeine 15mg tablets (Bristol Laboratories Ltd)
52085	Co-codamol 30mg/500mg effervescent tablets (Zanza Laboratories Ltd)
52216	Longtec 5mg modified-release tablets (Qdem Pharmaceuticals Ltd)
52217	Longtec 10mg modified-release tablets (Qdem Pharmaceuticals Ltd)
52220	Longtec 40mg modified-release tablets (Qdem Pharmaceuticals Ltd)
52495	Tramadol 50mg capsules (Bristol Laboratories Ltd)
52592	OxyNorm 10mg capsules (DE Pharmaceuticals)
52605	Tramadol 50mg capsules (Accord Healthcare Ltd)
52809	OxyContin 10mg modified-release tablets (Lexon (UK) Ltd)
52856	Co-codaprin 8mg/400mg tablets
52888	Codeine 15mg tablets (Kent Pharmaceuticals Ltd)
52889	Codeine 25mg/5ml oral solution (A A H Pharmaceuticals Ltd)
52929	Codeine 15mg tablets (Sigma Pharmaceuticals Plc)
52966	Generic Solpadeine Plus tablets
52977	Tramadol 100mg modified-release capsules (A A H Pharmaceuticals Ltd)
53079	Co-dydramol 10mg/500mg tablets (Sigma Pharmaceuticals Plc)
53113	OxyContin 10mg modified-release tablets (DE Pharmaceuticals)
53116	Longtec 20mg modified-release tablets (Qdem Pharmaceuticals Ltd)
53208	Co-proxamol 32.5mg/325mg tablets (Lexon (UK) Ltd)
53273	Morphine hydrochloride 10mg/5ml oral solution (Special Order)
53287	Co-codamol 30mg/500mg effervescent tablets (Alliance Healthcare (Distribution) Ltd)
53600	Codeine 60mg tablets (Alliance Healthcare (Distribution) Ltd)
53617	Ibuprofen and codeine 200mg+12.8mg Tablet (Almus Pharmaceuticals Ltd)
53639	Morphine 10mg modified-release tablets (Sigma Pharmaceuticals Plc)
53679	Co-codamol 30mg/500mg effervescent tablets (A A H Pharmaceuticals Ltd)
53702	Co-codamol 30mg/500mg tablets (Actavis UK Ltd)

prodcode	Product name
53709	Pethidine oral liquid
53999	Codeine phosphate 60mg Tablet (Wockhardt UK Ltd)
54017	Morphine sulphate Capsule
54023	Tramadol 50mg modified-release capsules (A A H Pharmaceuticals Ltd)
54085	Pethidine capsule
54354	Dihydrocodeine 30mg tablets (Kent Pharmaceuticals Ltd)
54520	Morphine sulphate Oral solution
54694	Longtec 80mg modified-release tablets (Qdem Pharmaceuticals Ltd)
54713	Dypracet 20mg/500mg tablets (Auden McKenzie (Pharma Division) Ltd)
54790	Pethidine 50mg tablets (Actavis UK Ltd)
54806	Transtec 52.5micrograms/hour transdermal patches (DE Pharmaceuticals)
54979	Fentanyl 50micrograms/hour transdermal patches (A A H Pharmaceuticals Ltd)
55044	Co-codamol 30mg/500mg caplets (Waymade Healthcare Plc)
55052	Morcap SR 50mg capsules (Hospira UK Ltd)
55206	Morphine 20mg modified-release capsules
55245	Co-proxamol 32.5mg/325mg tablets (Phoenix Healthcare Distribution Ltd)
55309	Codeine 15mg tablets (Phoenix Healthcare Distribution Ltd)
55425	Dihydrocodeine 10mg tablets
55465	Co-codamol 30mg/500mg capsules (Sigma Pharmaceuticals Plc)
55530	Co-dydramol 10mg/500mg tablets (Phoenix Healthcare Distribution Ltd)
55752	Fentanyl 100micrograms/hour transdermal patches (Phoenix Healthcare Distribution Ltd)
56006	Co-codamol 8mg/500mg tablets (Bristol Laboratories Ltd)
56022	Pethidine 50mg Capsule (Martindale Pharmaceuticals Ltd)
56171	Co-codamol 30mg/500mg capsules (Kent Pharmaceuticals Ltd)
56205	Boots Paracetamol and Codeine Extra capsules (The Boots Company Plc)
56266	Co-codamol 30mg/500mg tablets (Alliance Healthcare (Distribution) Ltd)
56340	Co-codamol 30mg/500mg caplets (J M McGill Ltd)
56461	Co-codamol 30mg/500mg tablets (Kent Pharmaceuticals Ltd)

prodcode	Product name
56491	Zamadol SR 200mg capsules (Lexon (UK) Ltd)
56549	Co-codamol 8mg/500mg effervescent tablets (Waymade Healthcare Plc)
56559	Codeine 30mg tablets (Phoenix Healthcare Distribution Ltd)
56565	Co-codamol 15mg/500mg tablets (A A H Pharmaceuticals Ltd)
56665	Oxylan 10mg modified-release tablets (Chanelle Medical UK Ltd)
56670	Fentanyl 25micrograms/hour transdermal patches (Sigma Pharmaceuticals Plc)
56671	BuTrans 5micrograms/hour transdermal patches (Waymade Healthcare Plc)
56788	Morphine sulfate 10mg/5ml oral solution (A A H Pharmaceuticals Ltd)
56817	Codeine 15mg tablets (Almus Pharmaceuticals Ltd)
57027	Pethidine 50mg tablets (A A H Pharmaceuticals Ltd)
57033	Oxylan 10mg modified-release tablets (Actavis UK Ltd)
57052	Oxylan 20mg modified-release tablets (Actavis UK Ltd)
57097	Co-codamol 30mg/500mg capsules (Alliance Healthcare (Distribution) Ltd)
57197	Co-dydramol 10mg/500mg tablets (Waymade Healthcare Plc)
57353	Co-codamol 30mg/500mg caplets (DE Pharmaceuticals)
57381	Codeine 60mg tablets (Teva UK Ltd)
57465	Co-codamol 8mg/500mg caplets (DE Pharmaceuticals)
57487	Codeine 30mg tablets (Waymade Healthcare Plc)
57839	Co-codamol 15mg/500mg tablets (Waymade Healthcare Plc)
57865	Co-codamol 30mg/500mg caplets (Actavis UK Ltd)
57900	Co-codamol 30mg/500mg caplets (A A H Pharmaceuticals Ltd)
57929	Co-codamol 8mg/500mg capsules (Waymade Healthcare Plc)
58039	Oxycodone 5mg/5ml oral solution
58114	Lynlor 20mg capsules (Actavis UK Ltd)
58129	Zeridame SR 100mg tablets (Actavis UK Ltd)
58217	Lynlor 5mg capsules (Actavis UK Ltd)
58288	Co-codamol 30mg/500mg capsules (DE Pharmaceuticals)
58316	Tramadol 50mg modified-release capsules (DE Pharmaceuticals)

prodcode	Product name
58493	Oxylan 20mg modified-release tablets (Chanelle Medical UK Ltd)
58501	Co-codamol 30mg/500mg caplets (AM Distributions (Yorkshire) Ltd)
58636	Co-codamol 8mg/500mg effervescent tablets (Teva UK Ltd)
58737	Pethidine 50mg tablets (Alliance Healthcare (Distribution) Ltd)
58766	BuTrans 10micrograms/hour transdermal patches (Waymade Healthcare Plc)
58828	Generic Migraleve tablets
58848	Dypracet 30mg/500mg tablets (Auden McKenzie (Pharma Division) Ltd)
58853	Lynlor 10mg capsules (Actavis UK Ltd)
58855	Co-codamol 30mg/500mg capsules (Waymade Healthcare Plc)
58879	Morphine hydrochloride 10mg/5ml oral solution
59057	Fentanyl 400microgram buccal films sugar free
59131	Co-codamol 8mg/500mg capsules (Bayer Plc)
59146	BuTrans 20micrograms/hour transdermal patches (Waymade Healthcare Plc)
59392	Hapoctasin 70micrograms/hour transdermal patches (Actavis UK Ltd)
59442	Co-codamol 30mg/500mg caplets (Phoenix Healthcare Distribution Ltd)
59443	Fentanyl 200microgram buccal films sugar free
59473	Hapoctasin 52.5micrograms/hour transdermal patches (Actavis UK Ltd)
59479	Co-codamol 30mg/500mg capsules (Actavis UK Ltd)
59482	Fentanyl 37.5microgram/hour transdermal patches
59490	Mezolar Matrix 37.5microgram/hour transdermal patches (Sandoz Ltd)
59584	Morphine sulfate 10mg/5ml oral solution (Alliance Healthcare (Distribution) Ltd)
59618	Transtec 35micrograms/hour transdermal patches (Mawdsley-Brooks & Company Ltd)
59705	Co-codamol 8mg/500mg capsules (DE Pharmaceuticals)
59865	Shortec 10mg capsules (Qdem Pharmaceuticals Ltd)
59978	Dihydrocodeine 30mg tablets (Waymade Healthcare Plc)
59986	Co-codamol 30mg/500mg tablets (M & A Pharmachem Ltd)
59989	Dihydrocodeine 30mg tablets (Ranbaxy (UK) Ltd)
60040	Generic Migraleve Pink tablets

prodcode	Product name
60053	Tephine 200microgram sublingual tablets (Sandoz Ltd)
60121	Tramadol 50mg modified-release capsules (Waymade Healthcare Plc)
60146	Shortec 5mg capsules (Qdem Pharmaceuticals Ltd)
60158	Shortec 20mg capsules (Qdem Pharmaceuticals Ltd)
60170	Hapoctasin 35micrograms/hour transdermal patches (Actavis UK Ltd)
60196	Oxylan 40mg modified-release tablets (Chanelle Medical UK Ltd)
60477	Fentanyl 25micrograms/hour transdermal patches (A A H Pharmaceuticals Ltd)
60517	Co-codamol 30mg/500mg effervescent tablets (Almus Pharmaceuticals Ltd)
60518	Morphine sulfate 500micrograms/5ml oral solution
60640	Codeine 15mg tablets (Waymade Healthcare Plc)
60751	Tilodol SR 200mg tablets (Sandoz Ltd)
60759	Tapentadol 20mg/ml oral solution sugar free
60766	Fentanyl 25micrograms/hour transdermal patches (Waymade Healthcare Plc)
60943	Transtec 35micrograms/hour transdermal patches (Sigma Pharmaceuticals Plc)
60950	Morphine sulfate 5mg/5ml oral solution
60958	Codeine 15mg tablets (DE Pharmaceuticals)
61086	Opiodur 12micrograms/hour transdermal patches (Pfizer Ltd)
61091	Codeine 60mg tablets (Waymade Healthcare Plc)
61100	Tephine 400microgram sublingual tablets (Sandoz Ltd)
61156	Fentanyl 12micrograms/hour transdermal patches (Waymade Healthcare Plc)
61272	Tramadol 50mg capsules (Phoenix Healthcare Distribution Ltd)
61305	Mylafent 75micrograms/hour transdermal patches (Generics (UK) Ltd)
61372	Co-dydramol 10mg/500mg tablets (Kent Pharmaceuticals Ltd)
61423	Morphine 30mg modified-release tablets (Sigma Pharmaceuticals Plc)
61610	Tramadol 50mg capsules (Morningside Healthcare Ltd)
61647	Co-codamol 15mg/500mg tablets (Alliance Healthcare (Distribution) Ltd)
61698	Co-dydramol 10mg/500mg/5ml oral solution
61708	Recivit 267microgram sublingual tablets (Grunenthal Ltd)

prodcode	Product name
61764	Palexia 20mg/ml oral solution (Grunenthal Ltd)
61775	Tramadol 50mg capsules (Sigma Pharmaceuticals Plc)
61779	Reltebon 40mg modified-release tablets (Actavis UK Ltd)
61836	Reltebon 20mg modified-release tablets (Actavis UK Ltd)
61935	Reltebon 10mg modified-release tablets (Actavis UK Ltd)
61936	Reltebon 5mg modified-release tablets (Actavis UK Ltd)
62169	Co-codamol 8mg/500mg tablets (Vantage)
62228	Codeine 30mg tablets (DE Pharmaceuticals)

Appendix 3 Anxiety medical codes

Read Code	Description	medcode
1466	H/O: anxiety state	3407
1B12.00	'Nerves' - nervousness	29608
1B12.11	'Nerves'	3586
1B12.12	Tension - nervous	514
1B13.00	Anxiousness	131
1B13.11	Anxiousness - symptom	5902
1B13.12	Anxious	93401
1B1V.00	C/O - panic attack	11890
2258	O/E - anxious	13124
2259	O/E - nervous	8725
225J.00	O/E - panic attack	19000
8G52.00	Antiphobic therapy	63521
8G94.00	Anxiety management training	9125
8HHp.00	Referral for guided self-help for anxiety	28925
E2...00	Neurotic; personality and other nonpsychotic disorders	9686
E20..00	Neurotic disorders	5249
E200.00	Anxiety states	636
E200000	Anxiety state unspecified	6939
E200100	Panic disorder	4069
E200111	Panic attack	462
E200200	Generalised anxiety disorder	4659
E200300	Anxiety with depression	655
E200400	Chronic anxiety	1758
E200500	Recurrent anxiety	4634
E200z00	Anxiety state NOS	4534
E201.00	Hysteria	2188
E201000	Hysteria unspecified	41572
E201100	Hysterical blindness	3438
E201200	Hysterical deafness	44739
E201300	Hysterical tremor	23598
E201400	Hysterical paralysis	34696
E201500	Hysterical seizures	16484
E201511	Fit - hysterical	33702
E201600	Other conversion disorder	15431
E201611	Astasia - abasia; hysterical	46399
E201612	Globus hystericus	4143
E201700	Hysterical amnesia	4269
E201800	Hysterical fugue	4775
E201900	Multiple personality	43302
E201A00	Dissociative reaction unspecified	23490
E201B00	Compensation neurosis	29322

Read Code	Description	medcode
E201C00	Phantom pregnancy	24525
E201z00	Hysteria NOS	23354
E201z11	Aphonia - hysterical	4105
E201z12	Ataxia - hysterical	24638
E201z13	Ganser's syndrome - hysterical	40066
E202.00	Phobic disorders	1907
E202.11	Social phobic disorders	16638
E202.12	Phobic anxiety	9944
E202000	Phobia unspecified	2300
E202100	Agoraphobia with panic attacks	3076
E202200	Agoraphobia without mention of panic attacks	12838
E202300	Social phobia; fear of eating in public	16199
E202400	Social phobia; fear of public speaking	31957
E202500	Social phobia; fear of public washing	18603
E202600	Acrophobia	28106
E202700	Animal phobia	28938
E202800	Claustrophobia	1723
E202900	Fear of crowds	31672
E202A00	Fear of flying	4167
E202B00	Cancer phobia	1510
E202C00	Dental phobia	2366
E202D00	Fear of death	10390
E202E00	Fear of pregnancy	6071
E202z00	Phobic disorder NOS	14729
E202z11	Weight fixation	38543
E203.00	Obsessive-compulsive disorders	3208
E203.11	Anancastic neurosis	47365
E203000	Compulsive neurosis	5678
E203100	Obsessional neurosis	2030
E203z00	Obsessive-compulsive disorder NOS	15566
E205.00	Neurasthenia - nervous debility	3361
E205.11	Nervous exhaustion	1582
E205.12	Tired all the time	7235
E206.00	Depersonalisation syndrome	5305
E207.00	Hypochondriasis	966
E20y.00	Other neurotic disorders	42000
E20y000	Somatization disorder	15321
E20y011	Briquet's disorder	56941
E20y100	Writer's cramp neurosis	3685
E20y200	Other occupational neurosis	39518
E20y300	Psychasthenic neurosis	72171
E20yz00	Other neurotic disorder NOS	43050
E20z.00	Neurotic disorder NOS	14780
E20z.11	Nervous breakdown	791
E26..00	Physiological malfunction arising from mental factors	4199

Read Code	Description	medcode
E260.00	Psychogenic musculoskeletal symptoms	44212
E260000	Psychogenic paralysis	48561
E260100	Psychogenic torticollis	56800
E260z00	Psychogenic musculoskeletal symptoms NOS	15035
E261.00	Psychogenic respiratory symptoms	38134
E261000	Psychogenic air hunger	32034
E261100	Psychogenic cough	15483
E261200	Psychogenic hiccough	47809
E261300	Psychogenic hyperventilation	20053
E261400	Psychogenic yawning	23413
E261500	Psychogenic aphonia	41615
E261z00	Psychogenic respiratory symptom NOS	34664
E262.00	Psychogenic cardiovascular symptoms	29448
E262000	Cardiac neurosis	15292
E262200	Neurocirculatory asthenia	15284
E262300	Psychogenic cardiovascular disorder	30961
E262z00	Psychogenic cardiovascular symptom NOS	15034
E263.00	Psychogenic skin symptoms	29461
E263000	Psychogenic pruritus	15959
E263z00	Psychogenic skin symptoms NOS	15224
E264.00	Psychogenic gastrointestinal tract symptoms	31422
E264.11	Globus abdominalis	37695
E264000	Psychogenic aerophagy	4963
E264011	Air swallowing - excessive	23774
E264200	Cyclical vomiting - psychogenic	2871
E264300	Psychogenic diarrhoea	15371
E264311	Spurious diarrhoea	10158
E264400	Psychogenic dyspepsia	3869
E264500	Psychogenic constipation	15939
E264z00	Psychogenic gastrointestinal tract symptom NOS	71437
E265.00	Psychogenic genitourinary tract symptoms	68379
E265100	Psychogenic vaginismus	20109
E265200	Psychogenic dysmenorrhea	44547
E265300	Psychogenic dysuria	55781
E265z00	Psychogenic genitourinary tract symptom NOS	73547
E267.00	Psychogenic symptom of special sense organ	89237
E26y.00	Other psychogenic malfunction	62400
E26y000	Bruxism (teeth grinding)	10001
E26yz00	Other psychogenic malfunction NOS	96391
E26z.00	Psychosomatic disorder NOS	5067
E278.00	Psychalgia	40311
E278000	Psychogenic pain unspecified	53766
E278100	Tension headache	191
E278111	Muscular headache	9999
E278200	Psychogenic backache	45205

Read Code	Description	medcode
E278z00	Psychalgia NOS	54373
E28..00	Acute reaction to stress	276
E28..11	Combat fatigue	43550
E280.00	Acute panic state due to acute stress reaction	11940
E281.00	Acute fugue state due to acute stress reaction	42737
E282.00	Acute stupor state due to acute stress reaction	15551
E283.00	Other acute stress reactions	38640
E283000	Acute situational disturbance	20245
E283100	Acute posttrauma stress state	24847
E283z00	Other acute stress reaction NOS	29707
E284.00	Stress reaction causing mixed disturbance of emotion/conduct	23869
E28z.00	Acute stress reaction NOS	26138
E28z.11	Examination fear	28129
E28z.12	Flying phobia	20802
E28z.13	Stage fright	27742
E29..00	Adjustment reaction	2826
E290000	Grief reaction	2775
E290011	Bereavement reaction	10734
E292.00	Adjustment reaction; predominant disturbance other emotions	24212
E292000	Separation anxiety disorder	6221
E292100	Adolescent emancipation disorder	23327
E292200	Early adult emancipation disorder	54658
E292300	Specific academic or work inhibition	62193
E292311	Specific academic or work inhibition	67304
E292312	Specific work inhibition	28302
E292400	Adjustment reaction with anxious mood	56924
E292500	Culture shock	58013
E292y00	Adjustment reaction with mixed disturbance of emotion	48588
E292z00	Adjustment reaction with disturbance of other emotion NOS	15665
E293.00	Adjustment reaction with predominant disturbance of conduct	16415
E293000	Adjustment reaction with aggression	6075
E293100	Adjustment reaction with antisocial behaviour	35914
E293200	Adjustment reaction with destructiveness	66398
E294.00	Adjustment reaction with disturbance emotion and conduct	45603
E29y.00	Other adjustment reactions	41455
E29y000	Concentration camp syndrome	53362
E29y100	Other post-traumatic stress disorder	32387
E29y200	Adjustment reaction with physical symptoms	35632
E29y300	Elective mutism due to an adjustment reaction	7716
E29y400	Adjustment reaction due to hospitalisation	27390
E29y500	Other adjustment reaction with withdrawal	19921
E29yz00	Other adjustment reactions NOS	23462
E29z.00	Adjustment reaction NOS	37669
E2y..00	Other specified neuroses or other mental disorders	50106
E2z..00	Neuroses or other mental disorder NOS	42410

Read Code	Description	medcode
Eu05400	[X]Organic anxiety disorder	20773
Eu34114	[X]Persistant anxiety depression	15220
Eu4..00	[X]Neurotic; stress - related and somoform disorders	23808
Eu40.00	[X]Phobic anxiety disorders	9386
Eu40000	[X]Agoraphobia	2571
Eu40011	[X]Agoraphobia without history of panic disorder	16729
Eu40012	[X]Panic disorder with agoraphobia	14890
Eu40100	[X]Social phobias	11602
Eu40112	[X]Social neurosis	42788
Eu40200	[X]Specific (isolated) phobias	9785
Eu40211	[X]Acrophobia	67965
Eu40212	[X]Animal phobias	18248
Eu40213	[X]Claustrophobia	11280
Eu40214	[X]Simple phobia	12635
Eu40300	[X]Needle phobia	12508
Eu40y00	[X]Other phobic anxiety disorders	27685
Eu40z00	[X]Phobic anxiety disorder; unspecified	34064
Eu40z11	[X]Phobia NOS	7222
Eu40z12	[X]Phobic state NOS	67898
Eu41.00	[X]Other anxiety disorders	5385
Eu41000	[X]Panic disorder [episodic paroxysmal anxiety]	8205
Eu41011	[X]Panic attack	6408
Eu41012	[X]Panic state	4081
Eu41100	[X]Generalized anxiety disorder	10344
Eu41111	[X]Anxiety neurosis	962
Eu41112	[X]Anxiety reaction	35825
Eu41113	[X]Anxiety state	50191
Eu41200	[X]Mixed anxiety and depressive disorder	11913
Eu41211	[X]Mild anxiety depression	7749
Eu41300	[X]Other mixed anxiety disorders	44321
Eu41y00	[X]Other specified anxiety disorders	24066
Eu41y11	[X]Anxiety hysteria	28167
Eu41z00	[X]Anxiety disorder; unspecified	23838
Eu41z11	[X]Anxiety NOS	25638
Eu42.00	[X]Obsessive - compulsive disorder	5304
Eu42.11	[X]Anankastic neurosis	24251
Eu42.12	[X]Obsessive-compulsive neurosis	21836
Eu42000	[X]Predominantly obsessional thoughts or ruminations	20634
Eu42100	[X]Predominantly compulsive acts [obsessional rituals]	22019
Eu42200	[X]Mixed obsessional thoughts and acts	18399
Eu42y00	[X]Other obsessive-compulsive disorders	38809
Eu42z00	[X]Obsessive-compulsive disorder; unspecified	22721
Eu43.00	[X]Reaction to severe stress; and adjustment disorders	11098
Eu43000	[X]Acute stress reaction	11607
Eu43011	[X]Acute crisis reaction	36374

Read Code	Description	medcode
Eu43012	[X]Acute reaction to stress	10535
Eu43013	[X]Combat fatigue	70779
Eu43014	[X]Crisis state	21559
Eu43015	[X]Psychic shock	7813
Eu43100	[X]Post - traumatic stress disorder	4171
Eu43111	[X]Traumatic neurosis	32182
Eu43200	[X]Adjustment disorders	11336
Eu43211	[X]Culture shock	36228
Eu43212	[X]Grief reaction	21197
Eu43213	[X]Hospitalism in children	41235
Eu43300	[X]Acute post-traumatic stress disorder follow military comb	101785
Eu43400	[X]Chron post-traumatic stress disorder follow military comb	101725
Eu43y00	[X]Other reactions to severe stress	21753
Eu43z00	[X]Reaction to severe stress; unspecified	31515
Eu44.00	[X]Dissociative [conversion] disorders	22136
Eu44.11	[X]Conversion hysteria	35311
Eu44.12	[X]Conversion reaction	52161
Eu44.13	[X]Hysteria	27588
Eu44000	[X]Dissociative amnesia	40994
Eu44100	[X]Dissociative fugue	39826
Eu44200	[X]Dissociative stupor	56141
Eu44300	[X]Trance and possession disorders	39747
Eu44400	[X]Dissociative motor disorders	34978
Eu44411	[X]Psychogenic aphonia	12147
Eu44412	[X]Psychogenic dysphonia	18801
Eu44500	[X]Dissociative convulsions	56966
Eu44511	[X]Pseudoseizures	11354
Eu44600	[X]Dissociative anaesthesia and sensory loss	27633
Eu44611	[X]Psychogenic deafness	50121
Eu44700	[X]Mixed dissociative [conversion] disorders	88758
Eu44y00	[X]Other dissociative [conversion] disorders	64166
Eu44y11	[X]Ganser's syndrome	46567
Eu44y12	[X]Multiple personality	39919
Eu44y13	[X]Psychogenic confusion	16988
Eu44y14	[X]Psychogenic twilight state	68259
Eu44z00	[X]Dissociative [conversion] disorder; unspecified	48906
Eu45.00	[X]Somatoform disorders	18049
Eu45000	[X]Somatization disorder	24439
Eu45011	[X]Multiple psychosomatic disorder	23704
Eu45012	[X]Briquet's syndrome	59682
Eu45100	[X]Undifferentiated somatoform disorder	57877
Eu45111	[X]Undifferentiated psychosomatic disorder	34735
Eu45200	[X]Hypochondriacal disorder	7537
Eu45211	[X]Body dysmorphic disorder	12626
Eu45212	[X]Dysmorphophobia nondelusional	30680

Read Code	Description	medcode
Eu45213	[X]Hypochondriacal neurosis	24264
Eu45214	[X]Hypochondriasis	10870
Eu45215	[X]Nosophobia	66806
Eu45300	[X]Somatoform autonomic dysfunction	41038
Eu45311	[X]Cardiac neurosis	44269
Eu45312	[X]Da Costa's syndrome	32632
Eu45313	[X]Gastric neurosis	63259
Eu45314	[X]Neurocirculatory asthenia	50793
Eu45316	[X]Psychogenic cough	12715
Eu45317	[X]Psychogenic diarrhoea	43316
Eu45318	[X]Psychogenic dyspepsia	16714
Eu45319	[X]Psychogenic dysuria	53122
Eu45320	[X]Psychogenic flatulence	47698
Eu45321	[X]Psychogenic hiccough	53737
Eu45322	[X]Psychogenic hyperventilat	12830
Eu45323	[X]Psychogenic freq micturit	17081
Eu45324	[X]Psychogenic IBS	16560
Eu45325	[X]Psychogenic pylorospasm	93067
Eu45400	[X]Persistent somatoform pain disorder	30179
Eu45411	[X]Psychalgia	54382
Eu45412	[X]Psychogenic backache	38521
Eu45413	[X]Psychogenic headache	29329
Eu45414	[X]Somatoform pain disorder	36040
Eu45500	[X]Globus pharyngeus	12453
Eu45511	[X]Globus hystericus	100086
Eu45y00	[X]Other somatoform disorders	62002
Eu45y11	[X]Psychogenic dysmenorrhoea	46925
Eu45y12	[X]Globus hystericus	20906
Eu45y13	[X]Psychogenic pruritis	16679
Eu45y14	[X]Psychogenic torticollis	36009
Eu45y15	[X]Teeth-grinding	47570
Eu45z00	[X]Somatoform disorder; unspecified	48671
Eu45z11	[X]Psychosomatic disorder NOS	19242
Eu46.00	[X]Other neurotic disorders	28090
Eu46000	[X]Neurasthenia	16561
Eu46011	[X]Fatigue syndrome	9656
Eu46100	[X]Depersonalization - derealization syndrome	9265
Eu46y00	[X]Other specified neurotic disorders	44331
Eu46y11	[X]Briquet's disorder	100116
Eu46y12	[X]Dhat syndrome	47367
Eu46y13	[X]Occupational neurosis; including writer's cramp	11339
Eu46y14	[X]Psychasthenia	61753
Eu46y15	[X]Psychasthenia neurosis	90597
Eu46y16	[X]Psychogenic syncope	44586
Eu46z00	[X]Neurotic disorder; unspecified	49628

Read Code	Description	medcode
Eu46z11	[X]Neurosis NOS	21431
Eu51511	[X]Dream anxiety disorder	17687
Eu93000	[X]Separation anxiety disorder of childhood	18032
Eu93100	[X]Phobic anxiety disorder of childhood	24351
Eu93200	[X]Social anxiety disorder of childhood	29907
Eu93y12	[X]Childhood overanxious disorder	61430
R2y2.00	[D]Nervousness	2509
R2y2.11	[D]Nerves	17853
R2y2.12	[D]Nervous tension	10723
Z4L1.00	Anxiety counselling	7999
ZS7C700	Post-traumatic mutism	99609

Headache and non-specific anxiety codes
Bruxism (teeth grinding)
Dental phobia
Fear of flying
Flying phobia
Muscular headache
Tension headache
Tired all the time
[X]Needle phobia
[X]Phobia NOS
[X]Psychogenic headache

Appendix 4 Depression medical codes

Read Code	medcode	Description
1465.00	2716	H/O: depression
1B17.00	1996	Depressed
1B17.11	4824	C/O - feeling depressed
1B1J.00	1449	Emotional problem
1B1J.11	3502	Emotional upset
1B1U.00	9796	Symptoms of depression
1B1U.11	10438	Depressive symptoms
1BO..00	6021	Mood swings
1BP0.00	59869	Loss of interest in previously enjoyable activity
1BQ..00	25435	Loss of capacity for enjoyment
1BT..00	10015	Depressed mood
1BT..11	8928	Low mood
1BT..12	26028	Sad mood
1BU..00	53148	Loss of hope for the future
1JJ..00	100977	Suspected depression
1S4..00	12416	Mood observations
1S40.00	48349	Dysphoric mood
2257.00	1908	O/E - depressed
388J.00	19630	Hospital anxiety and depression scale
388K.00	18315	Geriatric depression scale
388P.00	19409	HAD scale: depression score
388g.00	26817	Beck depression inventory second edition score
8O82.00	25832	Emotional and psychosocial support and advice
9H90.00	12399	Depression annual review
9H91.00	12122	Depression medication review
9H92.00	30405	Depression interim review
9HA0.00	42931	On depression register
9ON3.00	96504	Stress monitoring default
9ON4.00	35648	Stress monitoring 1st letter
9ON5.00	56220	Stress monitoring 2nd letter
9ON6.00	106542	Stress monitoring 3rd letter
9ON7.00	99737	Stress monitoring verbal inv.
9ON8.00	96503	Stress monitoring phone invite
9ON9.00	57856	Stress monitoring deleted
9ONA.00	37248	Stress monitoring check done
9ONZ.00	70751	Stress monitoring admin.NOS
9k4..00	30583	Depression - enhanced services administration
9k40.00	65435	Depression - enhanced service completed
E001300	27677	Presenile dementia with depression
E002100	21887	Senile dementia with depression
E112.00	10610	Single major depressive episode

Read Code	medcode	Description
E112.11	5879	Agitated depression
E112.12	6546	Endogenous depression first episode
E112.13	6950	Endogenous depression first episode
E112.14	595	Endogenous depression
E112000	34390	Single major depressive episode, unspecified
E112100	16506	Single major depressive episode, mild
E112200	15155	Single major depressive episode, moderate
E112300	15219	Single major depressive episode, severe, without psychosis
E112400	32159	Single major depressive episode, severe, with psychosis
E112500	43324	Single major depressive episode, partial or unspec remission
E112600	57409	Single major depressive episode, in full remission
E112z00	7011	Single major depressive episode NOS
E113.00	15099	Recurrent major depressive episode
E113.11	6932	Endogenous depression - recurrent
E113000	35671	Recurrent major depressive episodes, unspecified
E113100	29342	Recurrent major depressive episodes, mild
E113200	14709	Recurrent major depressive episodes, moderate
E113300	25697	Recurrent major depressive episodes, severe, no psychosis
E113400	24171	Recurrent major depressive episodes, severe, with psychosis
E113500	56273	Recurrent major depressive episodes,partial/unspec remission
E113600	55384	Recurrent major depressive episodes, in full remission
E113700	6482	Recurrent depression
E113z00	25563	Recurrent major depressive episode NOS
E118.00	10825	Seasonal affective disorder
E11y200	27491	Atypical depressive disorder
E11z100	3489	Rebound mood swings
E11z200	9183	Masked depression
E130.00	8478	Reactive depressive psychosis
E130.11	17770	Psychotic reactive depression
E135.00	1055	Agitated depression
E200300	655	Anxiety with depression
E204.00	1131	Neurotic depression reactive type
E204.11	2639	Postnatal depression
E283.00	38640	Other acute stress reactions
E283z00	29707	Other acute stress reaction NOS
E284.00	23869	Stress reaction causing mixed disturbance of emotion/conduct
E28z.00	26138	Acute stress reaction NOS
E290.00	1533	Brief depressive reaction
E290z00	36246	Brief depressive reaction NOS
E291.00	16632	Prolonged depressive reaction
E292.00	24212	Adjustment reaction, predominant disturbance other emotions
E292400	56924	Adjustment reaction with anxious mood
E292y00	48588	Adjustment reaction with mixed disturbance of emotion
E292z00	15665	Adjustment reaction with disturbance of other emotion NOS
E294.00	45603	Adjustment reaction with disturbance emotion and conduct

Read Code	medcode	Description
E2B..00	324	Depressive disorder NEC
E2B1.00	4323	Chronic depression
E2C4.00	41599	Mixed disturbance of conduct and emotion
E2C4z00	6121	Mixed disturbance of conduct and emotion NOS
Eu20400	20785	[X]Post-schizophrenic depression
Eu25100	11055	[X]Schizoaffective disorder, depressive type
Eu25111	35274	[X]Schizoaffective psychosis, depressive type
Eu25112	41022	[X]Schizophreniform psychosis, depressive type
Eu3..00	5726	[X]Mood - affective disorders
Eu32.00	4639	[X]Depressive episode
Eu32.11	9055	[X]Single episode of depressive reaction
Eu32.12	18510	[X]Single episode of psychogenic depression
Eu32.13	7604	[X]Single episode of reactive depression
Eu32000	11717	[X]Mild depressive episode
Eu32100	9211	[X]Moderate depressive episode
Eu32200	9667	[X]Severe depressive episode without psychotic symptoms
Eu32211	41989	[X]Single episode agitated depressn w'out psychotic symptoms
Eu32212	22806	[X]Single episode major depression w'out psychotic symptoms
Eu32213	59386	[X]Single episode vital depression w'out psychotic symptoms
Eu32300	12099	[X]Severe depressive episode with psychotic symptoms
Eu32311	24117	[X]Single episode of major depression and psychotic symptoms
Eu32312	52678	[X]Single episode of psychogenic depressive psychosis
Eu32313	24112	[X]Single episode of psychotic depression
Eu32314	28863	[X]Single episode of reactive depressive psychosis
Eu32400	10667	[X]Mild depression
Eu32500	98346	[X]Major depression, mild
Eu32600	98252	[X]Major depression, moderately severe
Eu32700	98414	[X]Major depression, severe without psychotic symptoms
Eu32800	98417	[X]Major depression, severe with psychotic symptoms
Eu32B00	103677	[X]Antenatal depression
Eu32y00	6854	[X]Other depressive episodes
Eu32y11	10720	[X]Atypical depression
Eu32y12	56609	[X]Single episode of masked depression NOS
Eu32z00	2970	[X]Depressive episode, unspecified
Eu32z11	543	[X]Depression NOS
Eu32z12	3291	[X]Depressive disorder NOS
Eu32z13	28248	[X]Prolonged single episode of reactive depression
Eu32z14	5987	[X] Reactive depression NOS
Eu33.00	3292	[X]Recurrent depressive disorder
Eu33.11	8851	[X]Recurrent episodes of depressive reaction
Eu33.12	19696	[X]Recurrent episodes of psychogenic depression
Eu33.13	8902	[X]Recurrent episodes of reactive depression
Eu33.14	28756	[X]Seasonal depressive disorder
Eu33.15	8826	[X]SAD - Seasonal affective disorder
Eu33000	29784	[X]Recurrent depressive disorder, current episode mild

Read Code	medcode	Description
Eu33100	29520	[X]Recurrent depressive disorder, current episode moderate
Eu33200	33469	[X]Recurr depress disorder cur epi severe without psyc sympt
Eu33211	11329	[X]Endogenous depression without psychotic symptoms
Eu33212	11252	[X]Major depression, recurrent without psychotic symptoms
Eu33213	29451	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu33214	73991	[X]Vital depression, recurrent without psychotic symptoms
Eu33300	47009	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu33311	23731	[X]Endogenous depression with psychotic symptoms
Eu33312	28677	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33313	32941	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33314	31757	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33315	16861	[X]Recurrent severe episodes of psychotic depression
Eu33316	37764	[X]Recurrent severe episodes/reactive depressive psychosis
Eu33400	22116	[X]Recurrent depressive disorder, currently in remission
Eu33y00	47731	[X]Other recurrent depressive disorders
Eu33z00	44300	[X]Recurrent depressive disorder, unspecified
Eu33z11	36616	[X]Monopolar depression NOS
Eu34.00	42857	[X]Persistent mood affective disorders
Eu34100	7953	[X]Dysthymia
Eu34111	8584	[X]Depressive neurosis
Eu34112	10290	[X]Depressive personality disorder
Eu34113	7737	[X]Neurotic depression
Eu34114	15220	[X]Persistant anxiety depression
Eu34y00	50243	[X]Other persistent mood affective disorders
Eu34z00	39767	[X]Persistent mood affective disorder, unspecified
Eu3y.00	28008	[X]Other mood affective disorders
Eu3y000	50998	[X]Other single mood affective disorders
Eu3y100	29921	[X]Other recurrent mood affective disorders
Eu3y111	19054	[X]Recurrent brief depressive episodes
Eu3yy00	29579	[X]Other specified mood affective disorders
Eu3z.00	37090	[X]Unspecified mood affective disorder
Eu4..00	23808	[X]Neurotic, stress - related and somoform disorders
Eu41200	11913	[X]Mixed anxiety and depressive disorder
Eu41211	7749	[X]Mild anxiety depression
Eu43.00	11098	[X]Reaction to severe stress, and adjustment disorders
Eu43000	11607	[X]Acute stress reaction
Eu43012	10535	[X]Acute reaction to stress
Eu43y00	21753	[X]Other reactions to severe stress
Eu43z00	31515	[X]Reaction to severe stress, unspecified
Eu53011	13307	[X]Postnatal depression NOS
Eu53012	4979	[X]Postpartum depression NOS
Eu92.11	91580	[X]Emotional behavioural problems
R007z14	7382	[D]Work stress
ZR2A.00	26224	Beck depression inventory
ZR2A.11	26080	BDI - Beck depression inventory

Read Code	medcode	Description
ZR2B.00	42839	Beck hopelessness scale
ZR2G.00	28442	Behaviour and mood disturbance scale
ZR2h.00	38058	Brief depression rating scale
ZR7..00	52655	Depression anxiety scale
ZR8..00	54999	Depression self rating scale
ZR8..11	56130	DSRS - Depression self rating scale
ZRBY.00	39446	Edinburgh postnatal depression scale
ZRBY.11	25238	EPDS - Edinburgh postnatal depression scale
ZRL6.00	26374	Geriatric depression scale
ZRL6.11	35320	GDS - Geriatric depression scale
ZRL6.12	39131	Geriatric depression score
ZRLU.00	42975	Hamilton rating scale for depression
ZRLU.11	42836	HAMD - Hamilton rating scale for depression
ZRLU.12	44927	HRSD - Hamilton rating scale for depression
ZRLfH00	55288	Health of the Nation Outcome Scale item 7 - depressed mood
ZRLfI00	96038	Health of the Nation Outcome Scale item 7 - depressed mood
ZRLn.00	59794	Hopelessness scale
ZRLr.00	19245	Hospital anxiety and depression scale
ZRLr.11	35398	HAD - Hospital anxiety and depression scale
ZRLr.12	24820	HADS - Hospital anxiety and depression scale
ZRVM.00	56034	Leeds scale for the self-assessment of anxiety & depression
ZRaH.00	34275	Mood affective checklist
ZRaH.11	64584	MACL - Mood affective checklist
ZRbS.00	94518	Positive and negative affect schedule
ZRby.00	44287	Profile of mood states
ZRby.11	100194	POMS - Profile of mood states
ZRrI.00	102465	Wakefield self-assessment depression inventory
ZRrY.00	89707	WHO depression scale
ZRrc.00	56982	Zung self-rating depression scale
ZRrc.11	37942	SDS - Zung self-rating depression scale
ZV11100	15117	[V]Personal history of affective disorder

Appendix 5 Antidepressant product codes

prodcode	Product name
3490	Amitriptyline 10mg / Perphenazine 2mg tablets
595	Amitriptyline 25mg / Perphenazine 2mg tablets
20571	Fluphenazine with nortriptyline 500microgramswith10mg Tablet
8493	Motipress tablets (Sanofi-Synthelabo Ltd)
2936	Motival 10mg/500microgram tablets (Sanofi)
7780	Nortriptyline 10mg / Fluphenazine 500microgram tablets
14578	Nortriptyline 30mg / Fluphenazine 1.5mg tablets
16323	Perphenazine 2mg with Amitriptyline 10mg tablet
6894	Perphenazine 2mg with Amitriptyline 25mg tablet
1453	Triptafen m 2mg+10mg Tablet (Goldshield Pharmaceuticals Ltd)
1208	Triptafen tablets (AMCo)
38827	Triptafen-M tablets (Mercury Pharma Group Ltd)
5712	Depixol 3mg tablets (Lundbeck Ltd)
3951	Fluanxol 1mg tablets (Lundbeck Ltd)
50592	Fluanxol 1mg tablets (Sigma Pharmaceuticals Plc)
59593	Fluanxol 500microgram tablets (Lexon (UK) Ltd)
3953	Fluanxol 500microgram tablets (Lundbeck Ltd)
600	Flupentixol 1mg tablets
5707	Flupentixol 3mg tablets
2275	Flupentixol 500microgram tablets
55620	Flupentixol Liquid
41731	Isocarboxazid 10mg Tablet (Cambridge Laboratories Ltd)
12207	Isocarboxazid 10mg tablets
9206	Manerix 150mg tablets (Meda Pharmaceuticals Ltd)
5832	Manerix 300mg tablets (Meda Pharmaceuticals Ltd)
12503	Marplan 10mg Tablet (Cambridge Laboratories Ltd)
2883	Moclobemide 150mg tablets
41747	Moclobemide 150mg tablets (Teva UK Ltd)
5187	Moclobemide 300mg tablets
3349	Nardil 15mg tablets (Archimedes Pharma UK Ltd)
10787	Parnate 10mg Tablet (Goldshield Pharmaceuticals Ltd)
4321	Phenelzine 15mg tablets
3783	Tranylcypromine 10mg tablets
41654	Tranylcypromine 10mg tablets (AMCo)
40494	Agomelatine 25mg tablets
52516	Alventa XL 150mg capsules (Consilient Health Ltd)
52074	Alventa XL 75mg capsules (Consilient Health Ltd)
61236	Bonilux XL 150mg capsules (Sandoz Ltd)
45664	Depefex XL 150mg capsules (Chiesi Ltd)
45959	Depefex XL 75mg capsules (Chiesi Ltd)
3391	Dutonin 100mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)

prodcode	Product name
4297	Dutonin 200mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
15163	Edronax 4mg tablets (Pfizer Ltd)
623	Efexor 37.5mg tablets (Wyeth Pharmaceuticals)
6274	Efexor 50mg tablets (Wyeth Pharmaceuticals)
9182	Efexor 75mg tablets (Wyeth Pharmaceuticals)
5710	Efexor XL 150mg capsules (Pfizer Ltd)
51280	Efexor XL 150mg capsules (Waymade Healthcare Plc)
1474	Efexor XL 75mg capsules (Pfizer Ltd)
43968	Foraven XL 75mg capsules (Forum Products Ltd)
6421	Mirtazapine 15mg orodispersible tablets
43253	Mirtazapine 15mg orodispersible tablets (A A H Pharmaceuticals Ltd)
43241	Mirtazapine 15mg orodispersible tablets (Aurobindo Pharma Ltd)
61856	Mirtazapine 15mg orodispersible tablets (Consilient Health Ltd)
43248	Mirtazapine 15mg orodispersible tablets (Focus Pharmaceuticals Ltd)
55482	Mirtazapine 15mg orodispersible tablets (Generics (UK) Ltd)
43246	Mirtazapine 15mg orodispersible tablets (Genus Pharmaceuticals Ltd)
58291	Mirtazapine 15mg orodispersible tablets (Pfizer Ltd)
43237	Mirtazapine 15mg orodispersible tablets (Teva UK Ltd)
6795	Mirtazapine 15mg tablets
43239	Mirtazapine 15mg tablets (A A H Pharmaceuticals Ltd)
53699	Mirtazapine 15mg tablets (Actavis UK Ltd)
59953	Mirtazapine 15mg tablets (Almus Pharmaceuticals Ltd)
46668	Mirtazapine 15mg tablets (Arrow Generics Ltd)
43242	Mirtazapine 15mg tablets (Genus Pharmaceuticals Ltd)
54342	Mirtazapine 15mg tablets (Medreich Plc)
54644	Mirtazapine 15mg tablets (Pfizer Ltd)
43257	Mirtazapine 15mg tablets (Teva UK Ltd)
16154	Mirtazapine 15mg/ml oral solution sugar free
53321	Mirtazapine 15mg/ml oral solution sugar free (A A H Pharmaceuticals Ltd)
61547	Mirtazapine 15mg/ml oral solution sugar free (DE Pharmaceuticals)
47966	Mirtazapine 15mg/ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)
6488	Mirtazapine 30mg orodispersible tablets
43250	Mirtazapine 30mg orodispersible tablets (A A H Pharmaceuticals Ltd)
53648	Mirtazapine 30mg orodispersible tablets (Actavis UK Ltd)
48185	Mirtazapine 30mg orodispersible tablets (Almus Pharmaceuticals Ltd)
59694	Mirtazapine 30mg orodispersible tablets (Phoenix Healthcare Distribution Ltd)
742	Mirtazapine 30mg tablets
47945	Mirtazapine 30mg tablets (A A H Pharmaceuticals Ltd)
40160	Mirtazapine 30mg tablets (Actavis UK Ltd)
54792	Mirtazapine 30mg tablets (Alliance Healthcare (Distribution) Ltd)
60538	Mirtazapine 30mg tablets (DE Pharmaceuticals)
56209	Mirtazapine 30mg tablets (Phoenix Healthcare Distribution Ltd)
6481	Mirtazapine 45mg orodispersible tablets
43235	Mirtazapine 45mg orodispersible tablets (A A H Pharmaceuticals Ltd)
43236	Mirtazapine 45mg orodispersible tablets (Actavis UK Ltd)

prodcode	Product name
43256	Mirtazapine 45mg orodispersible tablets (Focus Pharmaceuticals Ltd)
43247	Mirtazapine 45mg orodispersible tablets (Genus Pharmaceuticals Ltd)
43234	Mirtazapine 45mg orodispersible tablets (Teva UK Ltd)
6854	Mirtazapine 45mg tablets
33337	Mirtazapine 45mg tablets (A A H Pharmaceuticals Ltd)
58625	Mirtazapine 45mg tablets (Actavis UK Ltd)
59954	Mirtazapine 45mg tablets (Almus Pharmaceuticals Ltd)
4554	Nefazodone 100mg tablets
4011	Nefazodone 200mg tablets
9534	Nefazodone Starter pack
5611	Optimax 500mg tablets (Merck Serono Ltd)
20504	Optimax wv Tablet (E. Merck)
12221	Pacitron 500mg Tablet (Rorer Pharmaceuticals Ltd)
43673	Politid XL 150mg capsules (Actavis UK Ltd)
41299	Politid XL 75mg capsules (Actavis UK Ltd)
48199	Ranfaxine XL 75mg capsules (Ranbaxy (UK) Ltd)
2356	Reboxetine 4mg tablets
41314	Rodomel XL 150mg capsules (Teva UK Ltd)
41033	Rodomel XL 75mg capsules (Teva UK Ltd)
59753	Sunveniz XL 150mg tablets (Sun Pharmaceuticals UK Ltd)
60843	Sunveniz XL 75mg tablets (Sun Pharmaceuticals UK Ltd)
40817	Tardcaps XL 150mg capsules (IXL Pharma Ltd)
40815	Tardcaps XL 75mg capsules (IXL Pharma Ltd)
39809	Tifaxin XL 150mg capsules (Genus Pharmaceuticals Ltd)
39770	Tifaxin XL 75mg capsules (Genus Pharmaceuticals Ltd)
57751	Tonpular XL 150mg capsules (Wockhardt UK Ltd)
52716	Tonpular XL 75mg capsules (Wockhardt UK Ltd)
4422	Tryptophan 500mg tablets
40295	Valdoxan 25mg tablets (Servier Laboratories Ltd)
40514	Venaxx XL 150mg capsules (AMCo)
40515	Venaxx XL 75mg capsules (AMCo)
50081	Venlablue XL 150mg capsules (Bluefish Pharmaceuticals AB)
59035	Venlablue XL 37.5mg capsules (Bluefish Pharmaceuticals AB)
49511	Venlablue XL 75mg capsules (Bluefish Pharmaceuticals AB)
58726	Venladex XL 150mg tablets (Dexcel-Pharma Ltd)
55424	Venlafaxine
55501	Venlafaxine 150mg Modified-release capsule (Hillcross Pharmaceuticals Ltd)
2654	Venlafaxine 150mg modified-release capsules
60549	Venlafaxine 150mg modified-release capsules (Kent Pharmaceuticals Ltd)
43334	Venlafaxine 150mg modified-release capsules (Sandoz Ltd)
39360	Venlafaxine 150mg modified-release tablets
50934	Venlafaxine 150mg/5ml oral solution
40054	Venlafaxine 225mg modified-release tablets
45806	Venlafaxine 37.5mg modified-release tablets
301	Venlafaxine 37.5mg tablets

prodcode	Product name
56662	Venlafaxine 37.5mg tablets (A A H Pharmaceuticals Ltd)
59923	Venlafaxine 37.5mg tablets (Bristol Laboratories Ltd)
51361	Venlafaxine 37.5mg tablets (Ranbaxy (UK) Ltd)
60895	Venlafaxine 37.5mg tablets (Teva UK Ltd)
13237	Venlafaxine 37.5mg/5ml oral suspension
2617	Venlafaxine 50mg tablets
470	Venlafaxine 75mg modified-release capsules
59563	Venlafaxine 75mg modified-release capsules (Kent Pharmaceuticals Ltd)
43203	Venlafaxine 75mg modified-release capsules (Sandoz Ltd)
39359	Venlafaxine 75mg modified-release tablets
1222	Venlafaxine 75mg tablets
60449	Venlafaxine 75mg tablets (A A H Pharmaceuticals Ltd)
56457	Venlafaxine 75mg tablets (Teva UK Ltd)
53326	Venlafaxine 75mg/5ml oral solution
40062	Venlalic XL 150mg tablets (DB Ashbourne Ltd)
40407	Venlalic XL 225mg tablets (DB Ashbourne Ltd)
45818	Venlalic XL 37.5mg tablets (DB Ashbourne Ltd)
40059	Venlalic XL 75mg tablets (DB Ashbourne Ltd)
44936	Venlaneo XL 150mg capsules (Kent Pharmaceuticals Ltd)
44937	Venlaneo XL 75mg capsules (Kent Pharmaceuticals Ltd)
40092	Vensir XL 150mg capsules (Morningside Healthcare Ltd)
40277	Vensir XL 75mg capsules (Morningside Healthcare Ltd)
40517	Vexarin XL 150mg capsules (Generics (UK) Ltd)
42600	Vexarin XL 75mg capsules (Generics (UK) Ltd)
40764	ViePax 37.5mg tablets (Dexcel-Pharma Ltd)
40917	ViePax 75mg tablets (Dexcel-Pharma Ltd)
40049	ViePax XL 150mg tablets (Dexcel-Pharma Ltd)
40048	ViePax XL 75mg tablets (Dexcel-Pharma Ltd)
4726	Zispin 30mg tablets (Organon Laboratories Ltd)
60370	Zispin SolTab 15mg orodispersible tablets (Mawdsley-Brooks & Company Ltd)
6846	Zispin SolTab 15mg orodispersible tablets (Merck Sharp & Dohme Ltd)
50892	Zispin SolTab 15mg orodispersible tablets (Necessity Supplies Ltd)
10083	Zispin SolTab 30mg orodispersible tablets (Merck Sharp & Dohme Ltd)
53543	Zispin SolTab 30mg orodispersible tablets (Necessity Supplies Ltd)
15268	Zispin SolTab 45mg orodispersible tablets (Merck Sharp & Dohme Ltd)
648	Cipralex 10mg tablets (Lundbeck Ltd)
26056	Cipralex 10mg/ml oral drops (Lundbeck Ltd)
6360	Cipralex 20mg tablets (Lundbeck Ltd)
41062	Cipralex 20mg/ml oral drops (Lundbeck Ltd)
785	Cipralex 5mg tablets (Lundbeck Ltd)
3861	Cipramil 10mg tablets (Lundbeck Ltd)
1712	Cipramil 20mg tablets (Lundbeck Ltd)
2408	Cipramil 40mg tablets (Lundbeck Ltd)
815	Cipramil 40mg/ml drops (Lundbeck Ltd)
34498	Citalopram 10mg Tablet (Neo Laboratories Ltd)

prodcode	Product name
476	Citalopram 10mg tablets
34586	Citalopram 10mg tablets (A A H Pharmaceuticals Ltd)
32848	Citalopram 10mg tablets (Actavis UK Ltd)
49165	Citalopram 10mg tablets (Alliance Healthcare (Distribution) Ltd)
42660	Citalopram 10mg tablets (Almus Pharmaceuticals Ltd)
52100	Citalopram 10mg tablets (Arrow Generics Ltd)
59650	Citalopram 10mg tablets (Aurobindo Pharma Ltd)
53787	Citalopram 10mg tablets (Bristol Laboratories Ltd)
34436	Citalopram 10mg tablets (Generics (UK) Ltd)
33720	Citalopram 10mg tablets (IVAX Pharmaceuticals UK Ltd)
52408	Citalopram 10mg tablets (Kent Pharmaceuticals Ltd)
45286	Citalopram 10mg tablets (Niche Generics Ltd)
52824	Citalopram 10mg tablets (PLIVA Pharma Ltd)
59193	Citalopram 10mg tablets (Ranbaxy (UK) Ltd)
34499	Citalopram 10mg tablets (Sandoz Ltd)
60888	Citalopram 10mg tablets (Sigma Pharmaceuticals Plc)
41528	Citalopram 10mg tablets (Teva UK Ltd)
56355	Citalopram 10mg tablets (Waymade Healthcare Plc)
34413	Citalopram 10mg tablets (Zentiva)
54827	Citalopram 10mg/5ml oral suspension
34722	Citalopram 20mg Tablet (Neo Laboratories Ltd)
67	Citalopram 20mg tablets
34356	Citalopram 20mg tablets (A A H Pharmaceuticals Ltd)
34871	Citalopram 20mg tablets (Actavis UK Ltd)
53394	Citalopram 20mg tablets (Alliance Healthcare (Distribution) Ltd)
48026	Citalopram 20mg tablets (Almus Pharmaceuticals Ltd)
56009	Citalopram 20mg tablets (Arrow Generics Ltd)
58476	Citalopram 20mg tablets (Aurobindo Pharma Ltd)
52607	Citalopram 20mg tablets (Bristol Laboratories Ltd)
52354	Citalopram 20mg tablets (DE Pharmaceuticals)
34415	Citalopram 20mg tablets (Generics (UK) Ltd)
34970	Citalopram 20mg tablets (Niche Generics Ltd)
26016	Citalopram 20mg tablets (Sandoz Ltd)
34966	Citalopram 20mg tablets (Teva UK Ltd)
60568	Citalopram 20mg tablets (Waymade Healthcare Plc)
34822	Citalopram 20mg tablets (Zentiva)
43519	Citalopram 40mg Tablet (Neo Laboratories Ltd)
4770	Citalopram 40mg tablets
36746	Citalopram 40mg tablets (A A H Pharmaceuticals Ltd)
46977	Citalopram 40mg tablets (Actavis UK Ltd)
60839	Citalopram 40mg tablets (Almus Pharmaceuticals Ltd)
55033	Citalopram 40mg tablets (DE Pharmaceuticals)
34603	Citalopram 40mg tablets (Generics (UK) Ltd)
45223	Citalopram 40mg tablets (Niche Generics Ltd)
34466	Citalopram 40mg tablets (Sandoz Ltd)

prodcode	Product name
45304	Citalopram 40mg tablets (Teva UK Ltd)
46926	Citalopram 40mg tablets (Zentiva)
513	Citalopram 40mg/ml oral drops sugar free
57936	Citalopram 40mg/ml oral drops sugar free (A A H Pharmaceuticals Ltd)
56292	Citalopram 40mg/ml oral drops sugar free (Actavis UK Ltd)
603	Escitalopram 10mg tablets
20152	Escitalopram 10mg/ml oral drops sugar free
6218	Escitalopram 20mg tablets
40726	Escitalopram 20mg/ml oral drops sugar free
6405	Escitalopram 5mg tablets
12123	Faverin 100mg tablets (Abbott Healthcare Products Ltd)
2897	Faverin 50mg tablets (Abbott Healthcare Products Ltd)
33071	Felicium 20mg capsules (Opus Pharmaceuticals Ltd)
42499	Fluoxetine 10mg tablets
38890	Fluoxetine 20mg Capsule (Milpharm Ltd)
22	Fluoxetine 20mg capsules
19183	Fluoxetine 20mg capsules (A A H Pharmaceuticals Ltd)
45329	Fluoxetine 20mg capsules (Actavis UK Ltd)
60962	Fluoxetine 20mg capsules (Alliance Healthcare (Distribution) Ltd)
45247	Fluoxetine 20mg capsules (Fannin UK Ltd)
34288	Fluoxetine 20mg capsules (Generics (UK) Ltd)
34202	Fluoxetine 20mg capsules (Genus Pharmaceuticals Ltd)
34294	Fluoxetine 20mg capsules (IVAX Pharmaceuticals UK Ltd)
59358	Fluoxetine 20mg capsules (Milpharm Ltd)
42107	Fluoxetine 20mg capsules (Niche Generics Ltd)
62155	Fluoxetine 20mg capsules (Phoenix Healthcare Distribution Ltd)
19470	Fluoxetine 20mg capsules (Ranbaxy (UK) Ltd)
45224	Fluoxetine 20mg capsules (Sandoz Ltd)
34456	Fluoxetine 20mg capsules (Teva UK Ltd)
34849	Fluoxetine 20mg capsules (Tillomed Laboratories Ltd)
45316	Fluoxetine 20mg capsules (Wockhardt UK Ltd)
33410	Fluoxetine 20mg capsules (Zentiva)
60534	Fluoxetine 20mg dispersible tablets sugar free
2548	Fluoxetine 20mg/5ml oral solution
34216	Fluoxetine 20mg/5ml oral solution (A A H Pharmaceuticals Ltd)
42803	Fluoxetine 20mg/5ml oral solution (IVAX Pharmaceuticals UK Ltd)
60619	Fluoxetine 20mg/5ml oral solution (Kent Pharmaceuticals Ltd)
30258	Fluoxetine 20mg/5ml oral solution (Teva UK Ltd)
36893	Fluoxetine 20mg/5ml oral solution sugar free
4075	Fluoxetine 60mg capsules
34856	Fluoxetine 60mg capsules (Generics (UK) Ltd)
2290	Fluvoxamine 100mg tablets
48045	Fluvoxamine 100mg tablets (A A H Pharmaceuticals Ltd)
44861	Fluvoxamine 100mg tablets (Actavis UK Ltd)
43518	Fluvoxamine 100mg tablets (IVAX Pharmaceuticals UK Ltd)

prodcode	Product name
2880	Fluvoxamine 50mg tablets
4352	Lustral 100mg tablets (Pfizer Ltd)
1612	Lustral 50mg tablets (Pfizer Ltd)
62335	Olena 20mg dispersible tablets (AMCo)
14740	Oxactin 20mg capsules (Discovery Pharmaceuticals Ltd)
35021	Paroxetine 10mg tablets
59288	Paroxetine 10mg tablets (Actavis UK Ltd)
527	Paroxetine 10mg/5ml oral suspension sugar free
50	Paroxetine 20mg tablets
34419	Paroxetine 20mg tablets (A A H Pharmaceuticals Ltd)
32899	Paroxetine 20mg tablets (Actavis UK Ltd)
33978	Paroxetine 20mg tablets (Generics (UK) Ltd)
40892	Paroxetine 20mg tablets (Genus Pharmaceuticals Ltd)
34351	Paroxetine 20mg tablets (IVAX Pharmaceuticals UK Ltd)
55023	Paroxetine 20mg tablets (Medreich Plc)
1397	Paroxetine 30mg tablets
34587	Paroxetine 30mg tablets (A A H Pharmaceuticals Ltd)
40165	Paroxetine 30mg tablets (Actavis UK Ltd)
32546	Paxoran 10mg Tablet (Ranbaxy (UK) Ltd)
29756	Paxoran 20mg Tablet (Ranbaxy (UK) Ltd)
418	Prozac 20mg capsules (Eli Lilly and Company Ltd)
48220	Prozac 20mg capsules (Lexon (UK) Ltd)
61335	Prozac 20mg capsules (Mawdsley-Brooks & Company Ltd)
57532	Prozac 20mg capsules (Waymade Healthcare Plc)
252	Prozac 20mg/5ml liquid (Eli Lilly and Company Ltd)
4907	Prozac 60mg capsules (Eli Lilly and Company Ltd)
37256	Prozep 20mg/5ml oral solution (Chemidex Pharma Ltd)
33779	Prozit 20mg/5ml oral solution (Pinewood Healthcare)
29786	Ranflutin 20mg capsules (Ranbaxy (UK) Ltd)
35112	Seroxat 10mg tablets (GlaxoSmithKline UK Ltd)
841	Seroxat 20mg tablets (GlaxoSmithKline UK Ltd)
3601	Seroxat 20mg/10ml liquid (GlaxoSmithKline UK Ltd)
1575	Seroxat 30mg tablets (GlaxoSmithKline UK Ltd)
55537	Seroxat 30mg tablets (Lexon (UK) Ltd)
727	Sertraline 100mg tablets
55146	Sertraline 100mg tablets (A A H Pharmaceuticals Ltd)
61503	Sertraline 100mg tablets (Actavis UK Ltd)
59600	Sertraline 100mg tablets (Almus Pharmaceuticals Ltd)
54933	Sertraline 100mg tablets (PLIVA Pharma Ltd)
44944	Sertraline 100mg tablets (Teva UK Ltd)
49519	Sertraline 100mg/5ml oral suspension
54826	Sertraline 150mg/5ml oral suspension
488	Sertraline 50mg tablets
32401	Sertraline 50mg tablets (A A H Pharmaceuticals Ltd)
58723	Sertraline 50mg tablets (Accord Healthcare Ltd)

prodcode	Product name
42387	Sertraline 50mg tablets (Actavis UK Ltd)
45915	Sertraline 50mg tablets (Almus Pharmaceuticals Ltd)
58664	Sertraline 50mg tablets (Generics (UK) Ltd)
55488	Sertraline 50mg tablets (Teva UK Ltd)
7328	Sertraline 50mg/5ml oral suspension
21081	Amitriptyline 12.5mg / Chlordiazepoxide 5mg capsules
18342	Amitriptyline 25mg / Chlordiazepoxide 10mg capsules

Appendix 6 Benzodiazepine and anti-anxiety drugs

prodcode	Product name
9696	Alprazolam 250microgram tablets
11486	Alprazolam 500microgram tablets
21081	Amitriptyline 12.5mg / Chlordiazepoxide 5mg capsules
18342	Amitriptyline 25mg / Chlordiazepoxide 10mg capsules
12452	Anxon 15mg Capsule (Beecham Research Laboratories)
12130	Anxon 30mg Capsule (Beecham Research Laboratories)
36581	Atensine 10mg Tablet (Rorer Pharmaceuticals Ltd)
10954	Ativan 1mg Tablet (Wyeth Pharmaceuticals)
17830	Ativan 2.5mg Tablet (Wyeth Pharmaceuticals)
22424	Bromazepam 1.5mg tablets
55774	Bromazepam 3mg tablets
19941	Bromazepam 3mg tablets
9008	Buspar 10mg tablets (IXL Pharma Ltd)
49504	Buspar 10mg tablets (Lexon (UK) Ltd)
2394	Buspar 5mg tablets (IXL Pharma Ltd)
40153	Buspirone 10mg Tablet (Galen Ltd)
5385	Buspirone 10mg tablets
61443	Buspirone 10mg tablets (A A H Pharmaceuticals Ltd)
46847	Buspirone 10mg tablets (Actavis UK Ltd)
28880	Buspirone 5mg Tablet (Galen Ltd)
3574	Buspirone 5mg tablets
59095	Buspirone 5mg tablets (A A H Pharmaceuticals Ltd)
45275	Buspirone 5mg tablets (Actavis UK Ltd)
43240	Buspirone 5mg tablets (Generics (UK) Ltd)
22189	CHLORDIAZEPOXIDE
28321	CHLORDIAZEPOXIDE
20701	CHLORDIAZEPOXIDE
20692	CHLORDIAZEPOXIDE
18350	CLOBAZAM 1 MG SUS
10694	CLOBAZAM 2.5 MG CAP
15429	CLOBAZAM 5 MG CAP
3109	CLOBAZAM 5 MG TAB
29806	CLOBAZAM 7.5 MG CAP
25893	Centrax 10mg Tablet (Parke-davis Research Laboratories)
41574	Chlordiazepoxide 10mg Capsule (Approved Prescription Services Ltd)
41629	Chlordiazepoxide 10mg Capsule (DDSA Pharmaceuticals Ltd)
41581	Chlordiazepoxide 10mg Capsule (IVAX Pharmaceuticals UK Ltd)
41988	Chlordiazepoxide 10mg Tablet (DDSA Pharmaceuticals Ltd)
1463	Chlordiazepoxide 10mg capsules
45241	Chlordiazepoxide 10mg capsules (A A H Pharmaceuticals Ltd)
41583	Chlordiazepoxide 10mg capsules (Actavis UK Ltd)

prodcode	Product name
5294	Chlordiazepoxide 10mg tablets
3147	Chlordiazepoxide 10mg tablets
62270	Chlordiazepoxide 10mg tablets (A A H Pharmaceuticals Ltd)
40386	Chlordiazepoxide 25mg Tablet (DDSA Pharmaceuticals Ltd)
6516	Chlordiazepoxide 25mg tablets
8550	Chlordiazepoxide 25mg tablets
41606	Chlordiazepoxide 5mg Capsule (Approved Prescription Services Ltd)
34928	Chlordiazepoxide 5mg Capsule (DDSA Pharmaceuticals Ltd)
28879	Chlordiazepoxide 5mg Tablet (DDSA Pharmaceuticals Ltd)
2122	Chlordiazepoxide 5mg capsules
35936	Chlordiazepoxide 5mg capsules (A A H Pharmaceuticals Ltd)
41582	Chlordiazepoxide 5mg capsules (Actavis UK Ltd)
4543	Chlordiazepoxide 5mg tablets
6025	Chlordiazepoxide 5mg tablets
43438	Chlordiazepoxide 5mg tablets (A A H Pharmaceuticals Ltd)
8742	Clidinium bromide with Chlordiazepoxide tablets
52093	Clobazam 100mg/5ml oral suspension
3110	Clobazam 10mg capsules
3111	Clobazam 10mg tablets
46796	Clobazam 10mg/5ml oral solution
20966	Clobazam 10mg/5ml oral suspension
55481	Clobazam 10mg/5ml oral suspension sugar free
37696	Clobazam 2.5mg capsules
51425	Clobazam 2.5mg/5ml oral solution
52056	Clobazam 2.5mg/5ml oral suspension
41303	Clobazam 25mg/5ml oral solution
48010	Clobazam 25mg/5ml oral suspension
50389	Clobazam 4mg/5ml oral solution
52052	Clobazam 4mg/5ml oral suspension
46850	Clobazam 5mg/5ml oral solution
17054	Clobazam 5mg/5ml oral suspension
60320	Clobazam 5mg/5ml oral suspension (Special Order)
54759	Clobazam 5mg/5ml oral suspension sugar free
52680	Clobazam 7.5mg/5ml oral solution
816	Clonazepam 1mg/1ml solution for injection ampoules and diluent
4483	Clonazepam 2.5mg/ml drops sugar free
32500	Clonazepam 250micrograms/5ml oral solution
57664	Clonazepam 250micrograms/5ml oral suspension
2073	Clonazepam 2mg tablets
53739	Clonazepam 2mg tablets (Sigma Pharmaceuticals Plc)
13200	Clonazepam 2mg/5ml oral solution sugar free
50108	Clonazepam 2mg/5ml oral solution sugar free
34491	Clonazepam 2mg/5ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)
58460	Clonazepam 312.5micrograms/5ml oral suspension
61015	Clonazepam 500microgram oral lyophilisates sugar free

prodcode	Product name
1559	Clonazepam 500microgram tablets
58482	Clonazepam 500microgram tablets (A A H Pharmaceuticals Ltd)
59396	Clonazepam 500microgram tablets (Almus Pharmaceuticals Ltd)
61626	Clonazepam 500microgram tablets (Auden McKenzie (Pharma Division) Ltd)
53311	Clonazepam 500microgram tablets (Phoenix Healthcare Distribution Ltd)
45077	Clonazepam 500microgram/5ml Oral solution (Rosemont Pharmaceuticals Ltd)
47066	Clonazepam 500micrograms/5ml oral solution
48544	Clonazepam 500micrograms/5ml oral solution sugar free
14743	Clonazepam 500micrograms/5ml oral suspension
17637	Clonazepam 500micrograms/5ml solution sugar free
24519	DIAZEPAM
10909	DIAZEPAM S/R 10 MG CAP
3956	Dalmane 15mg capsules (Meda Pharmaceuticals Ltd)
3105	Dalmane 30mg capsules (Meda Pharmaceuticals Ltd)
54695	Diazepam 10mg Tablet (M & A Pharmachem Ltd)
9111	Diazepam 10mg capsules
1400	Diazepam 10mg tablets
41632	Diazepam 10mg tablets (A A H Pharmaceuticals Ltd)
34807	Diazepam 10mg tablets (Actavis UK Ltd)
62216	Diazepam 10mg tablets (Almus Pharmaceuticals Ltd)
34293	Diazepam 10mg tablets (Generics (UK) Ltd)
46913	Diazepam 10mg tablets (IVAX Pharmaceuticals UK Ltd)
34340	Diazepam 10mg tablets (Ranbaxy (UK) Ltd)
41607	Diazepam 10mg tablets (Teva UK Ltd)
51335	Diazepam 10mg/5ml oral solution
58959	Diazepam 10mg/5ml oral solution (AM Distributions (Yorkshire) Ltd)
12849	Diazepam 10mg/5ml oral suspension
9045	Diazepam 1mg/5ml suspension
53566	Diazepam 2.5mg/5ml oral solution
9430	Diazepam 2.5mg/5ml oral suspension
34876	Diazepam 2mg Tablet (Berk Pharmaceuticals Ltd)
28347	Diazepam 2mg Tablet (Crosspharma Ltd)
45135	Diazepam 2mg Tablet (M & A Pharmachem Ltd)
34561	Diazepam 2mg Tablet (Regent Laboratories Ltd)
3870	Diazepam 2mg capsules
46	Diazepam 2mg tablets
33672	Diazepam 2mg tablets (A A H Pharmaceuticals Ltd)
34524	Diazepam 2mg tablets (Actavis UK Ltd)
45313	Diazepam 2mg tablets (Almus Pharmaceuticals Ltd)
34338	Diazepam 2mg tablets (Generics (UK) Ltd)
34677	Diazepam 2mg tablets (IVAX Pharmaceuticals UK Ltd)
29945	Diazepam 2mg tablets (Ranbaxy (UK) Ltd)
34335	Diazepam 2mg tablets (Teva UK Ltd)
56236	Diazepam 2mg tablets (Wockhardt UK Ltd)
2352	Diazepam 2mg/5ml oral solution

prodcode	Product name
32853	Diazepam 2mg/5ml oral solution (Sandoz Ltd)
10274	Diazepam 2mg/5ml oral solution sugar free
53461	Diazepam 2mg/5ml oral solution sugar free (A A H Pharmaceuticals Ltd)
20968	Diazepam 2mg/5ml oral solution sugar free (Actavis UK Ltd)
51985	Diazepam 2mg/5ml oral suspension
3205	Diazepam 5mg
34892	Diazepam 5mg Tablet (Berk Pharmaceuticals Ltd)
34681	Diazepam 5mg Tablet (Crosspharma Ltd)
47	Diazepam 5mg tablets
34635	Diazepam 5mg tablets (A A H Pharmaceuticals Ltd)
32296	Diazepam 5mg tablets (Actavis UK Ltd)
60936	Diazepam 5mg tablets (Arrow Generics Ltd)
59407	Diazepam 5mg tablets (DE Pharmaceuticals)
34615	Diazepam 5mg tablets (Generics (UK) Ltd)
46966	Diazepam 5mg tablets (IVAX Pharmaceuticals UK Ltd)
45218	Diazepam 5mg tablets (Ranbaxy (UK) Ltd)
45244	Diazepam 5mg tablets (Sandoz Ltd)
57838	Diazepam 5mg tablets (Sovereign Medical Ltd)
34482	Diazepam 5mg tablets (Teva UK Ltd)
57749	Diazepam 5mg tablets (Waymade Healthcare Plc)
9065	Diazepam 5mg/5ml oral solution
42503	Diazepam 5mg/5ml oral solution (A A H Pharmaceuticals Ltd)
59122	Diazepam 5mg/5ml oral solution (AM Distributions (Yorkshire) Ltd)
34045	Diazepam 5mg/5ml oral solution (Sandoz Ltd)
7796	Dipotassium clorazepate 15mg capsules
7798	Dipotassium clorazepate 7.5mg capsules
23205	Dormonoct 1mg Tablet (Hoechst Marion Roussel)
484	Equagesic Tablet (Wyeth Pharmaceuticals)
12484	Equanil 200mg Tablet (Wyeth Pharmaceuticals)
12512	Equanil 400mg Tablet (Wyeth Pharmaceuticals)
36611	Euhypnos 10mg/5ml Oral solution (Pharmacia Ltd)
29441	Euhypnos forte 20mg Capsule (Pharmacia Ltd)
28703	Evacalm 5mg Tablet (Unimed Pharmaceuticals Ltd)
24422	FLURAZEPAM 10 MG TAB
12278	FLURAZEPAM 15 MG TAB
18928	FLURAZEPAM 30 MG TAB
14480	Flunitrazepam 1mg tablets
3950	Flurazepam 15mg capsules
7566	Flurazepam 30mg capsules
8487	Frisium 10mg Capsule (Aventis Pharma)
14388	Frisium 10mg tablets (Sanofi)
57510	Frisium 10mg tablets (Waymade Healthcare Plc)
18260	HALCION .12 MG TAB
14425	HALCION .25 MG TAB
23796	Ketazolam 15mg Capsule

prodcode	Product name
28360	Ketazolam 30mg Capsule
10409	LORAZEPAM .5 MG TAB
14417	LORAZEPAM 1 MG SUS
23002	LORAZEPAM 5 MG TAB
11958	Lexotan 1.5mg Tablet (Roche Products Ltd)
9721	Lexotan 3mg Tablet (Roche Products Ltd)
8913	Librium 10mg Capsule (ICN Pharmaceuticals France S.A.)
17294	Librium 10mg Tablet (ICN Pharmaceuticals France S.A.)
24599	Librium 10mg capsules (Meda Pharmaceuticals Ltd)
32231	Librium 25mg Tablet (ICN Pharmaceuticals France S.A.)
12477	Librium 5mg Capsule (ICN Pharmaceuticals France S.A.)
9048	Librium 5mg Tablet (ICN Pharmaceuticals France S.A.)
18125	Librium 5mg capsules (Meda Pharmaceuticals Ltd)
5150	Loprazolam 1mg tablets
41596	Loprazolam 1mg tablets (Zentiva)
21437	Loramet 1mg Capsule (Wyeth Pharmaceuticals)
1088	Lorazepam 1mg tablets
61450	Lorazepam 1mg tablets (A A H Pharmaceuticals Ltd)
41391	Lorazepam 1mg tablets (Arrow Generics Ltd)
36200	Lorazepam 1mg tablets (Generics (UK) Ltd)
45829	Lorazepam 1mg tablets (Sandoz Ltd)
33086	Lorazepam 1mg tablets (Teva UK Ltd)
39284	Lorazepam 1mg tablets (Thornton & Ross Ltd)
37745	Lorazepam 1mg/5ml oral solution
37566	Lorazepam 1mg/5ml oral suspension
2091	Lorazepam 2.5mg tablets
57268	Lorazepam 2.5mg tablets (Sandoz Ltd)
35932	Lorazepam 2.5mg tablets (Teva UK Ltd)
42814	Lorazepam 2.5mg tablets (Thornton & Ross Ltd)
46896	Lorazepam 500micrograms/5ml oral solution
13279	Lorazepam 500micrograms/5ml oral suspension
56551	Lorazepam 5mg/5ml oral solution
61886	Lorazepam 5mg/5ml oral suspension
3357	Lormetazepam 1mg Capsule
34534	Lormetazepam 1mg Tablet (Wyeth Pharmaceuticals)
3354	Lormetazepam 1mg tablets
34516	Lormetazepam 1mg tablets (Generics (UK) Ltd)
34692	Lormetazepam 1mg tablets (Genus Pharmaceuticals Ltd)
48517	Lormetazepam 1mg/5ml oral suspension
3687	Lormetazepam 500microgram tablets
34292	Lormetazepam 500microgram tablets (A A H Pharmaceuticals Ltd)
34642	Lormetazepam 500microgram tablets (Generics (UK) Ltd)
34361	Lormetazepam 500microgram tablets (Genus Pharmaceuticals Ltd)
10676	MEPROBAMATE 400 MG CAP
10790	Medazepam 10mg Capsule

prodcode	Product name
21464	Medazepam 5mg Capsule
3639	Meprobamate 200mg Tablet
2828	Meprobamate 400mg tablets
8464	Meprobamate with bendroflumethiazide Tablet
11326	Meprobamate with ethoheptazine citrate and aspirin Tablet
24642	Milonorm 400mg Tablet (Wallace Manufacturing Chemists Ltd)
3524	Mogadon 5mg Capsule (Roche Products Ltd)
7786	Mogadon 5mg Tablet (ICN Pharmaceuticals France S.A.)
19450	Mogadon 5mg tablets (Meda Pharmaceuticals Ltd)
41900	NITRAZEPAM
15492	Nitrados 5mg Tablet (Rorer Pharmaceuticals Ltd)
3686	Nitrazepam 10mg Tablet
7924	Nitrazepam 2.5mg/5ml oral suspension
61678	Nitrazepam 2mg/5ml oral suspension
2407	Nitrazepam 5mg Capsule
34964	Nitrazepam 5mg Tablet (Berk Pharmaceuticals Ltd)
34770	Nitrazepam 5mg Tablet (DDSA Pharmaceuticals Ltd)
35	Nitrazepam 5mg tablets
34408	Nitrazepam 5mg tablets (A A H Pharmaceuticals Ltd)
41385	Nitrazepam 5mg tablets (Actavis UK Ltd)
34806	Nitrazepam 5mg tablets (Generics (UK) Ltd)
46953	Nitrazepam 5mg tablets (Ranbaxy (UK) Ltd)
34686	Nitrazepam 5mg tablets (Teva UK Ltd)
34555	Nitrazepam 5mg tablets (Wockhardt UK Ltd)
9814	Nitrazepam 5mg/5ml oral suspension
10789	Nobrium 10mg Capsule (Roche Products Ltd)
10791	Nobrium 5mg Capsule (Roche Products Ltd)
18291	Noctamid 1mg Tablet (Schering Health Care Ltd)
12293	Normison 10mg Capsule (Wyeth Pharmaceuticals)
21454	Normison 20mg Capsule (Wyeth Pharmaceuticals)
7652	OXAZEPAM 15 MG CAP
25273	Oxanid 10mg Tablet (M A Steinhard Ltd)
41542	Oxazepam 10mg Tablet (IVAX Pharmaceuticals UK Ltd)
4566	Oxazepam 10mg tablets
36604	Oxazepam 10mg tablets (A A H Pharmaceuticals Ltd)
41531	Oxazepam 10mg tablets (Actavis UK Ltd)
41553	Oxazepam 10mg tablets (Thornton & Ross Ltd)
41601	Oxazepam 15mg Tablet (IVAX Pharmaceuticals UK Ltd)
4141	Oxazepam 15mg tablets
41411	Oxazepam 15mg tablets (A A H Pharmaceuticals Ltd)
41602	Oxazepam 15mg tablets (Actavis UK Ltd)
46946	Oxazepam 15mg tablets (Thornton & Ross Ltd)
4140	Oxazepam 30mg Capsule
8721	Oxazepam 30mg Tablet
24321	Paxane 30mg Capsule (M A Steinhard Ltd)

prodcode	Product name
37325	Remnos 10mg Tablet (DDSA Pharmaceuticals Ltd)
26496	Rivotril 1mg/1ml concentrate for solution for injection ampoules (Roche Products Ltd)
17038	Rivotril 2.5mg/1ml drops (Imported (Switzerland))
8029	Rivotril 2mg tablets (Roche Products Ltd)
10650	Rivotril 500microgram tablets (Roche Products Ltd)
2737	Rohypnol 1mg tablets (Roche Products Ltd)
33070	Solis 5mg Capsule (Galen Ltd)
23874	Somnite 2.5mg/5ml oral suspension (Norgine Pharmaceuticals Ltd)
27847	Surem 5mg Capsule (Galen Ltd)
24739	TEMAZEPAM
23493	TEMAZEPAM PLANPAK
31163	TEMAZEPAM S/F
13612	TEMAZEPAM UD 10ML 10 MG/5ML ELI
28058	TEMAZEPAM UD 5ML 10 MG/5ML ELI
27538	TRIAZOLAM
56781	Tapclob 10mg/5ml oral suspension (Martindale Pharmaceuticals Ltd)
54934	Tapclob 5mg/5ml oral suspension (Martindale Pharmaceuticals Ltd)
38418	Temazepam 10mg Capsule (Berk Pharmaceuticals Ltd)
41718	Temazepam 10mg Capsule (Hillcross Pharmaceuticals Ltd)
41516	Temazepam 10mg Tablet (IVAX Pharmaceuticals UK Ltd)
41562	Temazepam 10mg Tablet (Pharmacia Ltd)
33648	Temazepam 10mg Tablet (Wyeth Pharmaceuticals)
921	Temazepam 10mg capsules
20245	Temazepam 10mg gel-fill capsules
20	Temazepam 10mg tablets
34331	Temazepam 10mg tablets (A A H Pharmaceuticals Ltd)
45254	Temazepam 10mg tablets (Actavis UK Ltd)
56927	Temazepam 10mg tablets (Ethigen Ltd)
56811	Temazepam 10mg tablets (F.Maltby & Sons Ltd)
34508	Temazepam 10mg tablets (Generics (UK) Ltd)
45283	Temazepam 10mg tablets (Genus Pharmaceuticals Ltd)
34002	Temazepam 10mg tablets (IVAX Pharmaceuticals UK Ltd)
49589	Temazepam 10mg tablets (Sandoz Ltd)
34406	Temazepam 10mg tablets (Teva UK Ltd)
15110	Temazepam 10mg/5ml Oral solution (Generics (UK) Ltd)
780	Temazepam 10mg/5ml oral solution sugar free
32847	Temazepam 10mg/5ml oral solution sugar free (A A H Pharmaceuticals Ltd)
55836	Temazepam 10mg/5ml oral solution sugar free (Focus Pharmaceuticals Ltd)
27367	Temazepam 10mg/5ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)
7569	Temazepam 15mg capsules
38424	Temazepam 20mg Capsule (Berk Pharmaceuticals Ltd)
41653	Temazepam 20mg Capsule (Hillcross Pharmaceuticals Ltd)
36602	Temazepam 20mg Tablet (Pharmacia Ltd)
30779	Temazepam 20mg Tablet (Wyeth Pharmaceuticals)
2403	Temazepam 20mg capsules

prodcode	Product name
32320	Temazepam 20mg gel-fill capsules
1729	Temazepam 20mg tablets
41717	Temazepam 20mg tablets (A A H Pharmaceuticals Ltd)
46964	Temazepam 20mg tablets (Actavis UK Ltd)
34572	Temazepam 20mg tablets (Generics (UK) Ltd)
46078	Temazepam 20mg tablets (Genus Pharmaceuticals Ltd)
30985	Temazepam 20mg tablets (IVAX Pharmaceuticals UK Ltd)
60825	Temazepam 20mg tablets (Sandoz Ltd)
46939	Temazepam 20mg tablets (Teva UK Ltd)
10430	Temazepam 30mg capsules
8798	Temazepam gelthix 10mg Capsule (Pharmacia Ltd)
23120	Temazepam gelthix 15mg Capsule (Pharmacia Ltd)
12462	Temazepam gelthix 20mg Capsule (Pharmacia Ltd)
20801	Temazepam gelthix 30mg Capsule (Pharmacia Ltd)
7567	Temazepam planpak Capsule (Manufacturer unknown)
8303	Tenavoid Tablet (Edwin Burgess Ltd)
3973	Tensium 10mg tablets (DDSA Pharmaceuticals Ltd)
3250	Tranxene 15mg capsules (Boehringer Ingelheim Ltd)
7797	Tranxene 7.5mg capsules (Boehringer Ingelheim Ltd)
46909	Triazolam (roi) 125microgram Tablet
55303	Triazolam 0.125mg Tablet (Berk Pharmaceuticals Ltd)
41822	Triazolam 0.25mg Tablet (Berk Pharmaceuticals Ltd)
7571	Triazolam 125microgram Tablet
2404	Triazolam 250microgram Tablet
44302	Tropium 10mg tablets (Dr Reddy's Laboratories (UK) Ltd)
27880	Tropium 5mg capsules (Dr Reddy's Laboratories (UK) Ltd)
30273	Tropium 5mg tablets (Dr Reddy's Laboratories (UK) Ltd)
10402	Valium 10mg Tablet (Roche Products Ltd)
20164	Valium 2mg Capsule (Roche Products Ltd)
2401	Valium 2mg Tablet (Roche Products Ltd)
30321	Valium 2mg/5ml Oral solution (Roche Products Ltd)
19299	Valium 5mg Capsule (Roche Products Ltd)
4338	Valium 5mg Tablet (Roche Products Ltd)
10802	Xanax 250microgram tablets (Pfizer Ltd)
12598	Xanax 500microgram tablets (Pfizer Ltd)

Appendix 7 Pain codes

medcode	readcode	readterm
123	N131.00	Cervicalgia - pain in neck
154	N142.11	Low back pain
396	N05..11	Osteoarthritis
476	M160.00	Psoriatic arthropathy
639	N05z211	Elbow osteoarthritis NOS
658	N05z400	Osteoarthritis NOS, of the hand
665	N05z611	Knee osteoarthritis NOS
829	N11z.11	Osteoarthritis spine
844	N040.00	Rheumatoid arthritis
1145	7047000	Spinal myelography NEC
1192	SK10y00	Other neck injuries
1296	N053611	Patellofemoral osteoarthritis
1312	N05z712	Foot osteoarthritis NOS
1355	16A2.00	Stiff neck
1541	F301.00	Other specified trigeminal neuralgia
1598	A531.11	Post-herpetic neuralgia
1959	N05z412	Thumb osteoarthritis NOS
1963	N10z.00	Spondylitis NOS
2184	N100.00	Ankylosing spondylitis
2209	N05z511	Hip osteoarthritis NOS
2225	S30..00	Fracture of neck of femur
2229	N05zB00	Osteoarthritis NOS, of acromioclavicular joint
2342	F372.12	Diabetic neuropathy
2463	S570.00	Neck sprain
2487	N05zL00	Osteoarthritis NOS, of knee
2617	N135z12	Wry neck
3057	N05..00	Osteoarthritis and allied disorders
3147	N05z100	Osteoarthritis NOS, of shoulder region
3253	SJz..00	Nerve and spinal cord injury NOS
3288	S10A.00	Fracture of neck
3324	16C6.00	Back pain without radiation NOS
3370	N140.11	Spinal stenosis
3640	N13z.00	Cervical and neck disorders NOS
3763	16C5.00	C/O - low back pain
3814	N05zA00	Osteoarthritis NOS, of sternoclavicular joint
4186	N043.00	Juvenile rheumatoid arthritis - Still's disease
4353	N050.00	Generalised osteoarthritis - OA
4409	S10..12	Fracture of vertebra without spinal cord lesion
4446	SK10.00	Other face and neck injuries
4461	N053700	Localised osteoarthritis, unspecified, of the ankle and foot
4490	N05z411	Finger osteoarthritis NOS

medcode	readcode	readterm
4698	N240500	Fibrositis of neck
4878	N05z713	Toe osteoarthritis NOS
4967	N05z500	Osteoarthritis NOS, pelvic region/thigh
5002	F372.11	Diabetic polyneuropathy
5023	N142.13	Acute back pain - lumbar
5307	7043100	Closure of spinal myelomeningocele
5476	N12..13	Acute back pain - disc
5776	N05z.00	Osteoarthritis NOS
5802	N05z900	Osteoarthritis NOS, of shoulder
5840	N143.11	Acute back pain with sciatica
5916	N141.11	Acute back pain - thoracic
5923	N145.11	Acute back pain - unspecified
6188	1D21.12	C/O - a neck symptom
6581	F301z00	Trigeminal neuralgia NOS
6639	14G1.00	H/O: rheumatoid arthritis
6704	N145.12	Back pain, unspecified
6736	16A..00	Stiff neck symptom
6812	N05zJ00	Osteoarthritis NOS, of hip
6866	P113.00	Spinal meningocele
6887	N05zS00	Osteoarthritis NOS, of 1st MTP joint
6916	N040P00	Seronegative rheumatoid arthritis
7033	2H2D.00	O/E - neck joint abnormal
7116	ZV48.12	[V]Problems with neck
7429	N11..12	Osteoarthritis of spine
7584	F300.00	Post-herpetic trigeminal neuralgia
7736	F162.00	Subacute combined degeneration of spinal cord
7795	C106.12	Diabetes mellitus with neuropathy
7866	N05zF00	Osteoarthritis NOS, of MCP joint
8120	14N3000	H/O Spinal surgery
8202	N05zN00	Osteoarthritis NOS, of ankle
8255	S10..00	Fracture of spine without mention of spinal cord injury
8350	N040T00	Flare of rheumatoid arthritis
8812	SD0y100	Superficial injury of neck NOS
9010	N05zT00	Osteoarthritis NOS, of lesser MTP joint
9179	F151.00	Spinal muscular atrophy
9193	F336.00	Phantom limb syndrome
9544	B7F4000	Spinal meningioma
9649	N05zE00	Osteoarthritis NOS, of wrist
9681	N05zH00	Osteoarthritis NOS, of DIP joint of finger
9683	N135z11	Stiff neck NOS
9707	N047.00	Seropositive errosive rheumatoid arthritis
9760	14G2.00	H/O: osteoarthritis
9912	N140200	Lumbar spinal stenosis
10223	A531511	Postherpetic neuralgia
10231	16C9.00	Chronic low back pain

medcode	readcode	readterm
10252	S1...00	Fracture of neck and trunk
11032	N05zG00	Osteoarthritis NOS, of PIP joint of finger
11498	A531200	Postherpetic trigeminal neuralgia
11724	SF0..00	Crush injury, face, scalp and neck
11853	SJ...13	Spinal cord injuries
12019	N04X.00	Seropositive rheumatoid arthritis, unspecified
12189	16CA.00	Mechanical low back pain
12327	SR20.00	Dislocations, sprains and strains involving head with neck
12500	M160z00	Psoriatic arthropathy NOS
12864	SF02.00	Crush injury, neck
14799	SK10z00	Other face and neck injuries NOS
14882	16A3.00	Wry neck/torticollis
15052	N05z800	Osteoarthritis NOS, other specified site
15144	N05z600	Osteoarthritis NOS, of the lower leg
15178	R04zz00	[D]Head and neck symptoms NOS
15206	N05z311	Wrist osteoarthritis NOS
15212	S570000	Neck sprain, unspecified
15218	7041100	Open chordotomy of spinal cord NEC
15331	N140.00	Spinal stenosis, excluding cervical region
15434	F041.00	Intraspinal abscess
15441	N053100	Localised osteoarthritis, unspecified, of shoulder region
15447	N05z700	Osteoarthritis NOS, of ankle and foot
15622	7J42500	Spinal traction for fracture of spine NEC
15839	N051500	Localised, primary osteoarthritis of the pelvic region/thigh
16164	P25z.00	Spinal cord anomalies NOS
16183	1D21.00	Symptom: head/neck
16242	N053400	Localised osteoarthritis, unspecified, of the hand
16481	1475	H/O: trigeminal neuralgia
16491	C106.13	Diabetes mellitus with polyneuropathy
16664	R04..00	[D]Head and neck symptoms
16885	7J49.00	Denervation of spinal facet joint of vertebra
16961	16A3.12	Wry neck symptom
17067	F171100	Autonomic neuropathy due to diabetes
17092	N110.12	Osteoarthritis cervical spine
17180	A531500	Postzoster neuralgia
17194	F16..00	Other diseases of spinal cord
17216	F161000	Myelopathy due to acute infarction of spinal cord
17360	SK10800	Injury of muscle and tendon at neck level
18016	F336000	Phantom limb syndrome with pain
18112	N053800	Localised osteoarthritis, unspecified, of other spec site
18226	N14z.12	Spinal disorder NOS
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy
18602	N051F00	Localised, primary osteoarthritis of elbow
18826	N11D.00	Osteoarthritis of spine
19713	N05zC00	Osteoarthritis NOS, of elbow

medcode	readcode	readterm
20117	SE08.00	Other contusion neck
20472	N051800	Localised, primary osteoarthritis of other specified site
20626	N053500	Localised osteoarthritis, unspecified, pelvic region/thigh
20660	N051z00	Localised, primary osteoarthritis NOS
20930	SJ71.00	Injury of peripheral nerves of neck
20994	N13y200	Crick in neck
21088	7042100	Percutaneous chordotomy of spinal cord
21101	SK1x300	Multiple injuries of neck
21159	N051600	Localised, primary osteoarthritis of the lower leg
21288	7J3..11	Lumbar spinal cord operations
21350	N051400	Localised, primary osteoarthritis of the hand
21358	N040200	Rheumatoid arthritis of shoulder
21528	N054.00	Oligoarticular osteoarthritis, unspecified
21533	N043200	Pauciarticular juvenile rheumatoid arthritis
21655	7048100	Rhizotomy of spinal nerve root
22452	N11D200	Osteoarthritis of lumbar spine
23466	F04z.00	Intracranial or intraspinal abscess NOS
23638	N052400	Localised, secondary osteoarthritis of the hand
23676	N050200	Generalised osteoarthritis of multiple sites
23690	SJ8..00	Injury of nerves and spinal cord at neck level
23778	SJ9..00	Injury of nerves and spinal cord at thorax level
24022	N051100	Localised, primary osteoarthritis of the shoulder region
24152	N05z300	Osteoarthritis NOS, of the forearm
24200	N101.00	Spinal enthesopathy
24217	N051200	Localised, primary osteoarthritis of the upper arm
24486	SJ70.11	Head and neck superficial nerve injury
24571	F372200	Asymptomatic diabetic neuropathy
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
24796	16C4.00	Back pain worse on sneezing
24958	N051D00	Localised, primary osteoarthritis of the wrist
25284	S1z..00	Fracture of neck and trunk NOS
25576	S570z00	Neck sprain NOS
25793	N051700	Localised, primary osteoarthritis of the ankle and foot
26231	SJ3..11	Spinal plexus injury
27557	N043z00	Juvenile rheumatoid arthritis NOS
27603	N04..00	Rheumatoid arthritis and other inflammatory polyarthropathy
27834	N05zU00	Osteoarthritis NOS, of IP joint of toe
27972	N05zz00	Osteoarthritis NOS
28261	7J49500	Denervation of spinal facet joint of lumbar vertebra NEC
28567	F04..00	Intracranial and intraspinal abscesses
28823	N135.11	Contracture of neck
28853	N04y012	Fibrosing alveolitis associated with rheumatoid arthritis
28908	N051E00	Localised, primary osteoarthritis of toe
29633	7043200	Closure of spinal meningocele
30058	S10..11	Fracture of transverse process spine - no spinal cord lesion

medcode	readcode	readterm
30093	SJ3..00	Nerve roots and spinal plexus injuries
30160	SJ...00	Nerve and spinal cord injuries
31054	N040S00	Rheumatoid arthritis - multiple joint
31200	N053z00	Localised osteoarthritis, unspecified, NOS
31209	F396400	Myopathy due to rheumatoid arthritis
31360	N045500	Juvenile rheumatoid arthritis
31545	S112700	Cls spinal fracture with complete thorac cord lesion, T7-12
31790	F372.00	Polyneuropathy in diabetes
31857	Q204.00	Spine or spinal cord injury due to birth trauma
32009	SR10.00	Fractures involving head with neck
32063	S11..00	Fracture of spine with spinal cord lesion
32149	M160100	Distal interphalangeal psoriatic arthropathy
32839	N051.00	Localised, primary osteoarthritis
32891	N052800	Localised, secondary osteoarthritis of other specified site
33479	N052600	Localised, secondary osteoarthritis of the lower leg
33481	7049	Other destruction of spinal cord
33503	S100611	C6 vertebra closed fracture without spinal cord lesion
33535	F161500	Anterior spinal artery thrombosis
33574	N052100	Localised, secondary osteoarthritis of the shoulder region
33967	S100211	C2 vertebra closed fracture without spinal cord lesion
34023	N05zK00	Osteoarthritis NOS, of sacro-iliac joint
34035	N052700	Localised, secondary osteoarthritis of the ankle and foot
34116	L331.00	Cord tight round neck
34122	N053.00	Localised osteoarthritis, unspecified
34166	S10z.00	Fracture of spine without mention of spinal cord lesion NOS
34804	N053600	Localised osteoarthritis, unspecified, of the lower leg
34806	N051300	Localised, primary osteoarthritis of the forearm
34835	SJ2..00	Spinal cord injury without evidence of spinal bone injury
34867	N050z00	Generalised osteoarthritis NOS
34873	S100511	C5 vertebra closed fracture without spinal cord lesion
35117	N140z00	Spinal stenosis NOS
35527	N05z000	Osteoarthritis NOS, of unspecified site
35785	F372100	Chronic painful diabetic neuropathy
35849	S112.00	Closed fracture of thoracic spine with spinal cord lesion
35864	SJ70.12	Neck superficial nerve injury
36121	SDC0.00	Superficial injuries involving head with neck
36276	N043300	Monarticular juvenile rheumatoid arthritis
36327	N050100	Generalised osteoarthritis of the hand
36875	Z6G6200	Neck stretching
36974	P2y1.00	Congenital spinal cord anomaly
37315	F3y0.00	Diabetic mononeuropathy
37326	Syu1.00	[X]Injuries to the neck
38053	S100711	C7 vertebra closed fracture without spinal cord lesion
38631	N050000	Generalised osteoarthritis of unspecified site
40237	F292300	Cyst of the spinal meninges

medcode	readcode	readterm
40516	7J49z00	Denervation of spinal facet joint of vertebra NOS
40946	N100.11	Marie - Strumpell spondylitis
40972	N05zP00	Osteoarthritis NOS, of subtalar joint
41001	S490.12	Closed dislocation of neck
41031	16AZ.00	Stiff neck symptom NOS
41088	N052200	Localised, secondary osteoarthritis of the upper arm
41090	N054600	Oligoarticular osteoarthritis, unspecified, of lower leg
41147	N140000	Spinal stenosis of unspecified region
41378	N11D000	Osteoarthritis of cervical spine
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
41935	SJ80.00	Concussion and oedema of cervical spinal cord
41941	N040900	Rheumatoid arthritis of PIP joint of finger
41985	N054800	Oligoarticular osteoarthritis, unspecified, other spec sites
42002	7J47900	Spinal probing
42045	N052.00	Localised, secondary osteoarthritis
42299	N040800	Rheumatoid arthritis of MCP joint
42405	N045000	Juvenile ankylosing spondylitis
42561	S100111	C1 vertebra closed fracture - no spinal cord lesion
42755	L387.00	Spinal/epidural anesth-induced headache dur labour/delivery
43091	S112600	Cls spinal fracture with unspec thoracic cord lesion, T7-12
43577	N140800	Degenerative lumbar spinal stenosis
43786	S11..12	Fracture of vertebra with spinal cord lesion
44041	N052500	Localised, secondary osteoarthritis of pelvic region/thigh
44203	N040100	Other rheumatoid arthritis of spine
44249	SJ70.00	Head and neck superficial nerve injury
44743	N040000	Rheumatoid arthritis of cervical spine
44774	B925100	Neoplasm of uncertain behaviour of spinal cord
45142	P25y112	Myelodysplasia of spinal cord
45246	N12A.11	Post spinal surgery syndrome
45296	N130100	Degenerative cervical spinal stenosis
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
45679	7J49100	Denervation of spinal facet joint of cervical vertebra NEC
45815	N052300	Localised, secondary osteoarthritis of the forearm
45918	P25y200	Congenital anomaly of spinal meninges
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy
47024	N11D100	Osteoarthritis of thoracic spine
47409	C109B11	Type II diabetes mellitus with polyneuropathy
47831	N043100	Acute polyarticular juvenile rheumatoid arthritis
48078	F372000	Acute painful diabetic neuropathy
48124	R04z.00	[D]Other symptoms affecting head and neck
48214	N054000	Oligoarticular osteoarthritis, unspec, of unspecified sites
48651	SR30.00	Crushing injuries involving head with neck
48832	N040700	Rheumatoid arthritis of wrist
48940	P252.00	Congenital tethering of spinal cord
48958	S112100	Cls spinal fracture wth complete thoracic cord lesion,T1-6

medcode	readcode	readterm
49067	N040B00	Rheumatoid arthritis of hip
49545	N053000	Localised osteoarthritis, unspecified, of unspecified site
49567	S114000	Closed spinal fracture with unspecified lumbar cord lesion
49740	N11y100	Enterobacterial spondylitis
50241	G769.00	Anterior spinal and vertebral artery compression syndromes
50365	P113z00	Spinal meningocele NOS
50527	C10FB11	Type II diabetes mellitus with polyneuropathy
50813	C109A11	Type II diabetes mellitus with mononeuropathy
50848	N05z200	Osteoarthritis NOS, of the upper arm
50863	N040D00	Rheumatoid arthritis of knee
51238	N040K00	Rheumatoid arthritis of 1st MTP joint
51239	N040F00	Rheumatoid arthritis of ankle
51667	F292111	Spinal meningeal adhesions
51894	A985300	Gonococcal spondylitis
51916	SH14900	Deep full thickness burn of neck without loss of body part
52095	N054100	Oligoarticular osteoarthritis, unspecified, of shoulder
52139	Zw04300	[Q] Central spinal stenosis
52699	S100311	C3 vertebra closed fracture without spinal cord lesion
53184	N11D300	Osteoarthritis of spine NOS
53396	F290y00	Other spinal puncture reaction
53578	P111.00	Spinal hydromeningocele
53754	FyuA700	[X]Other specified diseases of spinal cord
53850	Syu1800	[X]Sprain/strain of joint/ligam of oth & unsp part of neck
53858	N054z00	Osteoarthritis of more than one site, unspecified, NOS
53904	SJ3z.00	Nerve root and spinal plexus injuries NOS
53929	P113000	Spinal meningocele of unspecified site
54143	B74y000	Lipoma of spinal column
54224	N051000	Localised, primary osteoarthritis of unspecified site
54350	N05zR00	Osteoarthritis NOS, of other tarsal joint
54854	SK1x100	Multiple superficial injuries of neck
54894	F336100	Phantom limb syndrome without pain
55195	S11z.00	Fracture of spine with spinal cord lesion NOS
55388	N05zQ00	Osteoarthritis NOS, of talonavicular joint
56003	ZV48500	[V]Sensory problem of neck or trunk
56202	Nyu1G00	[X]Seropositive rheumatoid arthritis, unspecified
57267	N054900	Oligoarticular osteoarthritis, unspecified, multiple sites
57534	L331z00	Cord tight round neck NOS
57632	F151z00	Spinal muscular atrophy NOS
57641	7041200	Myelotomy of spinal cord
57912	N052z00	Localised, secondary osteoarthritis NOS
58728	Syu1100	[X]Superficial injury of other parts of the neck
58996	SJ2z.00	Spinal cord injury without spinal bone injury NOS
59107	Nyu1300	[X]Other psoriatic arthropathies
59278	SJ21.11	Dorsal cord injury without spinal bone injury
59616	N054400	Oligoarticular osteoarthritis, unspecified, of hand

medcode	readcode	readterm
59637	N053200	Localised osteoarthritis, unspecified, of the upper arm
59738	N040500	Rheumatoid arthritis of elbow
59990	7G15.11	Sensory skin flap including to head or neck
59996	S101711	C7 vertebra open fracture without spinal cord lesion
60382	S101311	C3 vertebra open fracture without spinal cord lesion
60506	7048400	Destruction of spinal nerve root NEC
60537	N053300	Localised osteoarthritis, unspecified, of the forearm
60611	F041z00	Intraspinal abscess NOS
60615	S113.00	Open fracture of thoracic spine with spinal cord lesion
60687	SJA0.00	Concussion and oedema of lumbar spinal cord
61090	N11y000	Brucella spondylitis
61137	7G19.11	Local subcutaneous pedicle skin flap including to head/neck
61862	P113300	Lumbar spinal meningocele
62286	SJ21.00	Thoracic cord injury without spinal bone injury
62337	S110000	Cls spinal fracture with unspec cervical cord lesion, C1-4
62401	F371200	Polyneuropathy in rheumatoid arthritis
62548	Fyu0B00	[X]Intracranial+intraspinal abscess+granuloma in diseases CE
62612	N140100	Thoracic spinal stenosis
62660	7041000	Stereotactic chordotomy of spinal cord
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy
62719	S101611	C6 vertebra open fracture without spinal cord lesion
63198	N040A00	Rheumatoid arthritis of DIP joint of finger
63365	N040600	Rheumatoid arthritis of distal radio-ulnar joint
63452	7J42300	Spinal extension traction for fracture of spine
63752	ZV48.00	[V]Head, neck or trunk problems
64310	B74y200	Lipoma of spinal canal - intradural
65125	PE1..11	Congenital wry neck
65587	7J49300	Denervation of spinal facet joint of thoracic vertebra NEC
65630	F161100	Myelopathy due to arterial thrombosis of spinal cord
65748	N05zD00	Osteoarthritis NOS, of distal radio-ulnar joint
65804	L384100	Spinal/epidural anaesth-induced headache during puerp
66769	SF02z00	Crush injury, neck NOS
66902	7047100	Spinal manometry
67358	S100411	C4 vertebra closed fracture without spinal cord lesion
67389	S492300	Closed spinal dislocation with complete thoracic cord lesion
67831	7048011	Destruction of lesion of spinal nerve root
67980	F161200	Myelopathy due to oedema of spinal cord
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy
68648	N054500	Oligoarticular osteoarthritis, unspecified, of pelvis/thigh
68712	N052000	Localised, secondary osteoarthritis of unspecified site
68839	Syu1F00	[X]Other specified injuries of neck
69098	S101111	C1 vertebra open fracture without spinal cord lesion
69388	N130000	Idiopathic cervical spinal stenosis
69432	S111.00	Open fracture of cervical spine with spinal cord lesion
69652	SD0z100	Superficial injury of neck NOS, infected

medcode	readcode	readterm
69837	A940.12	Syphilitic posterior spinal sclerosis
69886	F201.00	Multiple sclerosis of the spinal cord
70109	F151300	X-linked bulbo-spinal atrophy
70138	7J49y00	Denervation of spinal facet joint of vertebra OS
70221	Nyu1200	[X]Other specified rheumatoid arthritis
70266	P25..00	Other specified spinal cord anomalies
70425	N05zM00	Osteoarthritis NOS, of tibio-fibular joint
70427	B74y100	Lipoma of spinal canal - extradural
70475	S112B00	Cls spinal # with incomplete thoracid cord lesion, T7-12 NOS
70572	F151000	Unspecified spinal muscular atrophy
70599	B74y300	Lipoma of spinal cord
70658	N040H00	Rheumatoid arthritis of talonavicular joint
70825	Syu1200	[X]Superficial injury of neck, part unspecified
71521	SJ22.00	Lumbar cord injury without spinal bone injury
71673	7040	Partial extirpation of spinal cord
71784	N040J00	Rheumatoid arthritis of other tarsal joint
71885	F292100	Spinal meningeal adhesions
71966	Syu3800	[X]Other injury of lumbar spinal cord
72109	N054700	Oligoarticular osteoarthritis, unspecified, of ankle/foot
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
72324	S11..11	Fracture of transverse process of spine + spinal cord lesion
72614	N140700	Idiopathic lumbar spinal stenosis
72711	S110600	Cls spinal fracture with unspec cervical cord lesion, C5-7
73015	2AD6.00	O/E - ciliospinal reflex -ve.
73166	P25y400	Spinal cord hypoplasia
73619	N040G00	Rheumatoid arthritis of subtalar joint
73730	N140400	Degenerative thoracic spinal stenosis
73764	F041200	Subdural intraspinal abscess
73786	SR10000	Closed fractures involving head with neck
73788	S114500	Closed spinal fracture with cauda equina lesion
88273	L331100	Cord tight round neck - delivered
91600	P113200	Thoracic spinal meningocele
91625	Zw04400	[Q] Lateral spinal stenosis
91943	C10EC11	Type I diabetes mellitus with polyneuropathy
93827	L331000	Cord tight round neck unspecified
93829	S491.12	Open dislocation of neck
93836	N140900	Iatrogenic lumbar spinal stenosis
94189	S115.00	Open fracture of lumbar spine with spinal cord lesion
94584	S117300	Open fracture of sacrum with other spinal cord injury
94588	Zw04500	[Q] Central and lateral spinal stenosis
94954	7G15200	Local sensory skin flap to head or neck
95351	C10FA11	Type II diabetes mellitus with mononeuropathy
95529	S114100	Closed spinal fracture with complete lumbar cord lesion
95591	P25y.00	Other specified anomalies of spinal cord
95615	F150.11	Infantile spinal muscular atrophy

medcode	readcode	readterm
96413	SF0z.00	Crush injury, face, scalp and neck NOS
96473	S117.00	Open fracture of sacrum with spinal cord lesion
96514	S110800	Cls spinal fracture with anterior cervcl cord lesion, C5-7
96880	M160.11	Psoriatic arthritis
97073	N054200	Oligoarticular osteoarthritis, unspecified, of upper arm
97105	7049y00	Other specified destruction of spinal cord
97120	S101211	C2 vertebra open fracture without spinal cord lesion
97345	SyuLC00	[X]Sequelae of unspecified injury of neck and trunk
97861	SP06300	Infected spinal fixation device
97870	N140A00	Lumbar spinal stenosis secondary to other disease
97899	2I21.00	O/E - sign - head/neck
98630	N140600	Thoracic spinal stenosis secondary to other disease
98833	Syu2B00	[X]Other and unspecified injuries of thoracic spinal cord
98874	Syu1900	[X]Other and unspecified injuries of cervical spinal cord
99151	S101511	C5 vertebra open fracture without spinal cord lesion
99231	C108B11	Type I diabetes mellitus with mononeuropathy
99397	S261600	Open fracture thumb proximal phalanx, neck
99414	N040L00	Rheumatoid arthritis of lesser MTP joint
99936	Syu1600	[X]Fracture of other parts of neck
100009	SJ90.00	Concussion and oedema of thoracic spinal cord
100102	Nyu5B00	[X]Spinal osteochondrosis, unspecified
100110	S110500	Cls spinal # with incomplete cervical cord lesion, C1-4 NOS
100378	Q204z00	Spine or spinal cord injury due to birth trauma NOS
100776	N040C00	Rheumatoid arthritis of sacro-iliac joint
100914	N040400	Rheumatoid arthritis of acromioclavicular joint
101311	C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
101525	Fyu3200	[X]Subacute combined degeneration/spinal cord in diseases CE
101956	S110B00	Cls spinal # with incomplete cervical cord lesion, C5-7 NOS
102012	Syu1A00	[X]Injury of other and unspecified nerves of neck
102043	S112A00	Cls spinal fracture with posterior thorac cord lesion, T7-12
102735	S110700	Cls spinal fracture with complete cervcl cord lesion, C5-7
102775	SJ21z00	Thoracic cord injury without spinal bone injury, NOS
7060	ZV57C00	[V]Palliative care
9755	8H7g.00	Referral to palliative care service
9996	Z172.00	Palliative care
10019	8BAP.00	Specialist palliative care
10784	8BAR.00	Specialist palliative care treatment - inpatient
11134	ZLD3R00	Discharge by palliative care physician
11318	8BAN.00	Community specialist palliative care
11978	ZL9AR00	Seen by palliative care physician
12739	8CM1.00	On gold standards palliative care framework
13628	ZL5AP00	Referral to palliative care physician
18551	8BJ1.00	Palliative treatment
19458	8CM3.00	Palliative care plan review
22288	8HH7.00	Referred to community specialist palliative care team

medcode	readcode	readterm
26354	8BAT.00	Specialist palliative care treatment - outpatient
28899	ZL18R00	Under care of palliative care physician
30643	9hB0.00	Excepted from palliative care quality indicators: Pat unsuit
48775	9Nh0.00	Under the care of community palliative care team
49651	8BAS.00	Specialist palliative care treatment - daycare
50291	8Hg0.00	Discharged from community specialist palliative care team
51219	ZLE6P00	Discharge from palliative care service
62309	9hB..00	Exception reporting: palliative care quality indicators
73313	9b9B.00	Palliative medicine
93845	9hB1.00	Excepted from palliative care quality indicators: Inform dis
16547	K58y000	Other pelvic pain - female
9811	R090G11	[D] Pelvic pain
2781	1A59.00	C/O pelvic pain
4706	N33A000	Bony pelvic pain
3297	SP2y200	Postoperative pain
5796	SP2y211	Post-operative pain
16558	M07z.12	Infected skin ulcer
62265	8CV2.00	Leg ulcer compression therapy started
9881	M271200	Mixed diabetic ulcer - foot
12764	7G2EC00	Three layer compression bandage for skin ulcer
101006	39C8.00	EPUAP (European pressure ulcer advisory panel) grade 2 ulcer
49675	9NM5.00	Attending leg ulcer clinic
65704	C109412	Type 2 diabetes mellitus with ulcer
5961	14F3.00	H/O: chronic skin ulcer
109100	9ks..00	Complex skin ulcer care enhanced services administration
11624	M271300	Arterial leg ulcer
6862	M270.00	Decubitus (pressure) ulcer
49640	2G5W.00	O/E - left chronic diabetic foot ulcer
8709	2G55.00	O/E - Left foot ulcer
32006	M271.14	Neurogenic leg ulcer
6308	M271.12	Ischaemic leg ulcer
105150	M270500	Stage II decubitus ulcer
5057	M271.11	Foot ulcer
99855	M271700	Neuropathic foot ulcer
6654	81H1.00	Dressing of ulcer
108537	M270.14	Decubitus ulcer and pressure area
5855	M271500	Venous ulcer of leg
8801	M271400	Mixed venous and arterial leg ulcer
93878	C10E511	Type I diabetes mellitus with ulcer
100778	39C7.00	EPUAP (European pressure ulcer advisory panel) grade 1 ulcer
106686	M270600	Stage III decubitus ulcer
85835	9N0t.00	Seen in primary care leg ulcer clinic
7093	2G54.00	O/E - Right foot ulcer
101713	M270200	Community hospital acquired pressure ulcer
15506	7G2E500	Dressing of skin ulcer NEC

medcode	readcode	readterm
51957	C108511	Type I diabetes mellitus with ulcer
104552	M270z00	Decubitus ulcer and pressure area NOS
1216	M271.13	Leg ulcer NOS
35316	2G5H.00	O/E - Right diabetic foot - ulcerated
100864	39C9.00	EPUAP (European pressure ulcer advisory panel) grade 3 ulcer
35116	2G5L.00	O/E - Left diabetic foot - ulcerated
5790	M271600	Traumatic leg ulcer
11264	G837.00	Venous ulcer of leg
44443	C108500	Insulin dependent diabetes mellitus with ulcer
104691	8CS3.00	Agreeing on leg ulcer treatment plan
49074	C10F400	Type 2 diabetes mellitus with ulcer
18683	C10E500	Type 1 diabetes mellitus with ulcer
14838	M271.15	Trophic leg ulcer
3928	M271.00	Non-pressure ulcer lower limb
4487	4JG3.00	Skin ulcer swab taken
22204	Z1B2300	Dressing of skin ulcer
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer
104850	M270400	Stage I decubitus ulcer and pressure area
24327	M271000	Ischaemic ulcer diabetic foot
9180	M27..00	Chronic skin ulcer
106902	M270700	Stage IV decubitus ulcer
100638	39CA.00	EPUAP (European pressure ulcer advisory panel) grade 4 ulcer
16856	A056.00	Amoebic skin ulceration
104293	M273.00	Non-healing leg ulcer
3929	M27z.00	Chronic skin ulcer NOS
55220	ZQ39.11	Decubitus ulcer assessment
91646	C10F411	Type II diabetes mellitus with ulcer
68390	C108512	Type 1 diabetes mellitus with ulcer
17787	7G2EA00	Two layer compression bandage for skin ulcer
19230	14F5.00	H/O: venous leg ulcer
104565	M274.00	Recurrent leg ulcer
62384	2G5V.00	O/E - right chronic diabetic foot ulcer
105031	8CMT.00	Leg ulcer care pathway
55075	C109411	Type II diabetes mellitus with ulcer
98704	C10E512	Insulin dependent diabetes mellitus with ulcer
19395	8HTh.00	Referral to leg ulcer clinic