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DRUG UTILISATION IN PATIENTS WITH KNEE OSTEOARTHRITIS AND THE ASSOCIATED RISK OF FALLS: A POPULATION BASED STUDY

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I Abstract

Background

Osteoarthritis is a chronic musculoskeletal condition that affects around 8 million people in the UK. It results in pain and disability that compromise quality of life and has substantial societal and economic burdens. Osteoarthritis can affect any joint, however, knees are most commonly affected, and the prevalence increases with age. Management involves non-pharmacological approaches such as exercise and weight control, and pharmacological approaches including prescribing analgesics. Recently a role of antidepressants and antiepileptic drugs (AEDs) was suggested in osteoarthritis related pain based on findings confirming the involvement of central sensitisation and neuropathic pain mechanisms. Patients with osteoarthritis use various analgesics and for varying periods, which may subject them to adverse drug events such as falls. Falls are a major public health concern in the UK and worldwide. Patients with osteoarthritis might be at an increased risk of falls due to joint pathology and chronic pain, coupled with age related physiological changes. However, in the UK, data on drug utilisation and the associated outcomes in patients with osteoarthritis are limited.

This research aimed to describe the utilisation of several analgesic drug classes including antidepressants, antiepileptic drugs (AEDs), opioids, NSAIDs and paracetamol in patients with knee osteoarthritis (KOA), and examine the association between analgesic use and the risk of falls.

Methods

Data were obtained from the Clinical Practice Research Datalink (CPRD), and the Hospital Episode Statistics. The study selected patients with a diagnosis of KOA from CPRD and measured the incidence of diagnosed KOA in primary care between 2000 and 2015. Subsequently, a cross-sectional analysis described the temporal changes in the utilisation of analgesic drug classes in patients with KOA between 2000 and 2015. This was followed by a cohort study on the patterns of analgesic use at an individual patient level. The association between analgesic use and the risk of fall within one year of KOA diagnosis was examined using two cohort studies. Analgesic use was treated as a time fixed exposure in the first analysis and as a time varying variable in the second analysis.

Results

A cohort of 137,051 patients with KOA was selected from CPRD. The annual incidence of KOA diagnosis in the years 2000 and 2015 was 1.33 and 1.47 patients per 1000 CPRD registrants, respectively.

The cross-sectional analysis showed a steady increase in the prescribing of all analgesic drugs classes, except for NSAIDs. In particular, the use of opioids was most prevalent in every study year. Tramadol was the most commonly prescribed opioid, with the number of defined daily doses (DDD) increasing from 0.11 to 0.64 DDDs per 1000 registrants per day between 2000 and 2015. Similarly, there was an increase in the oral morphine equivalent dose from 32.6 to 71.7 mg per day between 2000 and 2015. AEDs showed a marked increase in the number of new users doubled from 0.1 to 0.2 per 1000 registrants from 2000 to 2015. Variable proportions of patients used respective analgesic classes persistently during the first year after prescribing, between 36% (antidepressants) and 15% (opioids).

A significant association between any analgesic use and the risk of fall was found with HR (95% CI) 1.89 (1.66, 2.16) adjusted for age, gender and use of fall risk increasing drugs (FRIDs). Additionally, the study found that compared to those not using any analgesic, patients using three analgesic groups (neuropathic pain medications, opioids and non opioid analgesics) were at more than three times the risk of falling HR (95%CI) 3.24 (2.77, 3.78) adjusted for age, gender and use of FRIDs. The time varying analysis showed that current use of analgesics was associated with a greater risk of fall compared to periods of no analgesic use. The reported HR (95%CI) were 2.68 (2.14, 3.36), 2.22 (1.70, 2.91), 1.96 (1.70, 2.26), 1.47 (1.21, 1.78), 1.92 (1.63, 2.26) for antidepressants, AEDs, opioids, NSAIDs and paracetamol, respectively, adjusted for age, gender and use of FRIDs.

Conclusion

The study showed an overall increase in the prescribing of analgesic medicines in patients with KOA, with opioids being the most prevalent during the period between 2000 and 2015. The greatest increase in prescribing over time was observed in AEDs. The use of analgesics was associated with a significant risk of fall within a year after diagnosis of KOA. These findings inform policy and practice on the safety of analgesics in patients with KOA and identify this group of patients as a priority for administration of fall prevention programs/interventions.

II Presentations

Aqila Taqi, Harmony Otete, Roger Knaggs.

Long Term Opioid Prescribing in Primary Care Patients with Knee Osteoarthritis.

Poster presentation at the Arthritis Research UK, Pain Centre, Nottingham Scientific Advisory Board Meeting, Nottingham, United Kingdom, 21st November 2018.

Aqila Taqi, Harmony Otete, Roger Knaggs.

Long Term Opioid Prescribing in Primary Care Patients with Knee Osteoarthritis.

Poster presentation at the 34th International Conference of Pharmacoepidemiology & Therapeutic Risk Management (ICPE), Prague, Czech Republic, 18th August 2018.

Aqila Taqi, Harmony Otete, Roger Knaggs.

Drug Utilisation in Patients with Knee Osteoarthritis: A population Based Study.

Poster presentation at the 2nd Scientific Symposium of Omani Scholars, University of Leeds, Leeds, United Kingdom, 13th March 2018.

Aqila Taqi, Harmony Otete, Roger Knaggs.

Trends in Opioid Prescribing in Primary Care Patients with Knee Osteoarthritis.

Poster presentation at the 20th Annual European Congress of The International Society for Pharmacoeconomics and Outcomes Research (ISPOR),Glasgow, Scotland, 4thNovember 2017.

Aqila Taqi, Sonia Gran, Roger Knaggs.

Association between Analgesic Use and the Risk of Falls in Primary Care Patients with Knee Osteoarthritis.

Oral presentation at the Continuous Professional Development Program for Pharmacists (lecture series), Sultan Qaboos University, Pharmacy Department, Muscat, Sultanate Oman, 20th December 2018.

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IV List of Abbreviations

A&E	Accident and Emergency
AED	Anti-Epileptic Drugs
BNF	British National Formulary
CNCP	Chronic Non-Cancer Pain
COPD	Chronic Obstructive Pulmonary Disease
COX	Cyclo-Oxygenase Inhibitors
CPRD	Clinical Practice Research Datalink
DDD	Defined Daily Dose
DH	Department of Health
FRIDs	Fall Risk Increasing Drugs
GP	General Practice/Practitioners
HES	Hospital Episode Statistics
HR	Hazard Ratio
ICD-10	International Classification of Diseases - Tenth Revision
ISAC	Independent Scientific Advisory Committee
JNC	The Joint National Committee
MAOI	Monoamine Oxidase Inhibitor
MHRA	Medicines and Healthcare Product Regulatory Agency
MSK	Musculoskeletal
NDD	Numeric Daily Dose
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Nonsteroidal Anti-Inflammatory Drug
OARSI	Osteoarthritis Research Society International
OMEQ	Oral Morphine Equivalent Dose
OR	Odds Ratio
OTC	Over the Counter
PHE	Public Health England
QOF	Quality and Outcomes Framework
QOL	Quality of Life
RCT	Randomized Controlled Trial
SNRI	Serotonin Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressants
UK	United Kingdom
US	United States of America
WHO	World Health Organisation
95% CI	95% Confidence Interval

V Table of Contents

VI List of Tables

VII List of Figures

Chapter 1 Introduction

Musculoskeletal conditions (MSK) are chronic conditions that affect muscles, bones and joints and collectively, are the leading contributor to disability worldwide (WHO, 2019). These conditions are characterised by pain and reduced physical function, often leading to significant mental health decline, increased risk of developing other chronic health conditions and increased all-cause mortality (Briggs et al., 2015). MSK conditions can broadly be grouped as inflammatory conditions such as rheumatoid arthritis, conditions of MSK pain such as osteoarthritis (OA) and back pain, and osteoporosis and fragility fractures. In the UK, It is estimated that around 17 million people are affected by MSK conditions (Versus Arthritis, 2019).

Of the MSK disorders, OA represents the most common form of joint diseases, affecting more than 8 million people in the UK (Jordan et al., 2010). Osteoarthritis constitutes a substantial burden on the society and the wider economy and was the leading cause of lost workdays in 2018 (Versus Arthritis, 2019).

The condition can affect any joint, however, the knee joint is most commonly involved with 18.2% of people aged over 45 years in England being affected (Versus Arthritis, 2019). Patients with knee osteoarthritis (KOA) are largely treated in primary care using non-pharmacological and pharmacological management approaches. Non-pharmacological management includes exercise and weight control in addition to patient education, whereas the

pharmacological management involves prescribing analgesics (Mora et al., 2018).

Treatment guidelines recommend analgesics including paracetamol, NSAIDs and opioids, prescribed in an incremental approach according to pain intensity and individual patient's risk factors (NICE, 2014b). Recent evidence confirmed that OA related pain results from both, the usual nociceptive pain mechanisms in addition to the more complex central sensitisation and neuropathic pain (NP) mechanisms (Dimetroulas et al., 2014). Drugs recommended for neuropathic pain conditions include antidepressants such as amitriptyline and duloxetine, and anti-epileptic drugs (AEDs) including gabapentin and pregabalin (NICE, 2013). Although not included in many OA management guidelines, the NP medications are commonly prescribed for patients with chronic non cancer pain (CNCP) conditions including OA, as an off-label use (Montastruc et al., 2018).

Research showed that patients with KOA use several analgesics and for varying periods of time in their search for pain relief and joint function restoration, as currently no disease modifying treatments are available (Wilson et al., 2015). However, despite the high prevalence of KOA in the UK, and the common use of different analgesics among the affected patients, data on the prescribing prevalence of analgesics, antidepressants and AEDs in patients with KOA are sparse. Moreover, population level data on the patterns of drug use in patients with KOA have not been comprehensively described and pharmacoepidemiologic studies of temporal changes in prescribing trends are limited.

Drug utilisation studies apply pharmacoepidemiologic measures to estimate drug prescribing prevalence and analyse any relevant associated clinical outcomes. The overall aim of such studies is to inform prescribing prevalence at a population level, describe changing trends and patterns of use. Eventually these studies inform the overall rational use of drugs or raise any concerns on the safety of drug use (WHO, 2003).

Previous studies on drug utilisation in patients with OA/KOA, differed in the number and types of studied drugs, data sources and used to describe the utilisation patterns. Many studies were limited to describing patterns without addressing any relevant clinical outcomes associated with drugs' use.

In common with older people, patients with KOA are at risk of various adverse drug events, as a result of age-related physiological changes and a high prevalence of comorbidities (Dhalwani et al., 2017). However, due to the joint pathology and chronic pain, patients with KOA might be at a greater risk of certain adverse events such as falls (Dore et al., 2015).

Falls represent a public health concern both worldwide and, in the UK, (WHO, 2007). They are the leading cause of injury among those age 65 years and over, resulting in serious clinical consequences including hospitalisation and mortality (WHO, 2007). Falls are associated with several risk factors including non-modifiable risk factors e.g. old age, and modifiable factors such as medication use. Several medication classes were implicated such as psychotropic drugs including antipsychotics, sedatives and benzodiazepines (Seppala et al., 2018c). Medication use was recognised as a risk factor for falls, however, previous research showed inconsistent

results on the association between analgesic use and the risk of fall. Moreover, there is a paucity in studies investigating the association between current analgesic use and the risk of fall in patients with KOA.

Information on clinical outcomes associated with drug use is of high relevance and importance; with current national prescribing data indicated rising trends in prescribing opioids, antidepressants and AEDs (Zin et al., 2014, Moore at al.2009, Montastruc et al., 2018).

The present research project describes trends and patterns in the utilisation of five drug classes in patients with KOA namely: antidepressants, antiepileptic drugs (AEDs), opioids, Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol and investigated the association between exposure to these drug classes and the risk of fall in patients with KOA.

The study used data from the Clinical Practice Research Datalink (CPRD) and the hospital episode statistics (HES) databases. The use of CPRD, a primary care database with a large volume of high-quality data on patients broadly representative of UK population, enabled a detailed description of patterns of drug utilisation, quantification of cumulative exposure in terms of Defined Daily Doses (DDD) at a population level as well as individual patient level. To investigate the association between analgesic use and the risk of fall the study used records of patients with linkage to HES data.

The first two chapters provide an overview with sequential logic to establish the whole PhD research background and data sources.

The third chapter describes the process of the study cohort selection, which was based on a logical approach in applying Read code lists in a manner that avoided both over and underestimation of true numbers of patients with KOA.

Chapter 4 includes a cross sectional study over 16 years to capture overall drug utilisation by calendar years. It applied various drug utilisation measures to estimate prevalence and incidence of prescribing over time. Defined daily doses (DDD) per 1000 CPRD registrants were calculated in each calendar year between 2000 and 2015 and for all study drug classes.

Subsequently, in chapter 5 exposure to each drug class was quantified in terms of intensity of treatment at an individual patient's level. This was achieved through measuring the cumulative exposure to analgesics as (DDD per patient per year) during the first year after respective therapy initiation. The proportion of persistent users within each drug class was determined based on the cumulative exposure and the distribution of prescriptions through the quarters of the year.

The work in chapter 6 focused on comparing fall recording in the CPRD and HES datasets and subsequently informed the decision about the database to use for further analyses within this project.

In chapters 7 and 8 the association between drug utilisation and the risk of falls was investigated using two separate analytical approaches. In the first analysis, the association between analgesic use (treated as a time fixed exposure) and the risk of fall was quantified for any analgesic use and for multiple analgesics use. Additionally, the association of drug use was

treated as a time varying exposure and the risk of fall was compared between periods of current analgesic use and no current use.

Finally, in chapter 9, the final chapter of this thesis, a general discussion, implications for both practice and research and a conclusion. Chapters 3-8 open with a brief introduction including specific objectives followed by methods applied, results and a discussion section specific to each study.

Chapter 2 Literature Review

2.1 Osteoarthritis

2.1.1 Definition

Osteoarthritis is a chronic musculoskeletal condition that is a result of mechanical and biological events that destabilise the normal processes of cartilage degradation and synthesis within the joint. The condition involves the whole joint structure and it is clinically characterised by joint pain, stiffness and functional limitation (Glyn-Jones et al., 2015).

2.1.2 Pathophysiology

Osteoarthritis is a complex disorder of synovial joints affecting the structure of the entire joint involving not only the cartilage but also the joint lining, ligaments and underlying bone. It is now viewed as a metabolically dynamic process characterised by an imbalance of joint breakdown in association with a maladaptive and inadequate repair process. The disease presents as degeneration, destruction and eventual loss of articular cartilage centred on load-bearing areas and associated with osteophyte formation, remodelling of subarticular bone, weakening of periarticular muscles, ligamentous laxity, synovial inflammation and thickening of joint capsule (Hunter, 2014). Unlike inflammatory arthritis, inflammation in OA is chronic and of low grade with synovitis (infiltration of inflammatory cells into the synovium) being present even in the early stages of the disease (Heidari, 2011).

Osteoarthritis can arise in any synovial joint in the body, but most commonly affected are the knee, hip and spinal joints, as well as the small joints of the hand. There is no single aetiology for OA, and the exact causes are not known. Several biological and mechanical factors (see section 2.1.6) contribute to the development of OA (Silverwood et al., 2015).

The knee is a weight bearing joint and is the largest synovial joint in humans. (Silverwood et al., 2015). Unfortunately, due to the high use and stress of this joint it is a frequent site for painful conditions (Hunter, 2014). Knee is the most commonly affected joint and is considered to produce the greatest disability (Cross et al., 2014).

2.1.3 Diagnosis and Severity Grading

The diagnosis of OA (including KOA) is established on clinical grounds based on history and physical examination and there isn't a need for a routine investigation. Clinically, OA/KOA is characterised by pain, stiffness, cracking of the joint and loss of joint function which can eventually lead to disability (Shane Anderson and Loeser, 2010). The pain is usually associated with activity, however, pain at rest or at night is encountered in advanced OA. Joint movement becomes restricted and accompanied by functional difficulties such as knee locking (Shane Anderson and Loeser, 2010).

According to the NICE recommendations, the diagnosis of OA is given if a person: a) is aged 45 years or over and b) suffers an activity related joint pain and c) has a short duration (<30 minutes) joint related stiffness or

morning stiffness (NICE, 2014b). The diagnosis can be confirmed by plain X-ray radiographs, which may demonstrate structural abnormalities including joint space narrowing and osteophyte formation (Conaghan, 2012). As the disease progresses, pathological change in severe condition results in radiological changes that can be graded using the Kellgren and Lawrence (K&L) radiographic grading scheme (Kellgren and Lawrence, 1957). The widely used K&L scale, first described in 1957, ranges from 0 to 4 with radiologic OA defined as a score higher than 2, and severe radiological OA as a score higher than 3 in the left and/or right joint (Table 2-1)(Arden and Nevitt, 2006).

Table 2-1 Kellgren and Lawrence Criteria for The Severity of Osteoarthritis

Severity	**Criteria**
Grade 0	Absence of any sign of radiological OA;
Grade 1	Doubtful narrowing of joint space and possible osteophyte lipping
Grade 2	Definite osteophytes and possible narrowing of joint space
Grade 3	Moderate multiple osteophytes, definite narrowing of joint space, and some sclerosis and possible deformity of bone ends
Grade 4	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends

However, radiographic changes are not always accompanied by symptoms of pain, stiffness or loss of function; and conversely joint pain is not always associated with radiological abnormalities (Glyn-Jones et al., 2015). Several studies showed that the amount of joint deformity does not reliably predict the intensity of pain a person may experience as demonstrated by radiographic studies (Cubukcu et al., 2012). The clinical severity of KOA can

be measured using disease specific tools such as the algofunctional index of Lequesne and the Western Ontario and McMaster Universities OA index (WOMAC). The WOMAC is widely used and measures three separate dimensions; pain, stiffness and function and has two versions a visual analogue scale and a Likert scale (McConnell et al., 2001).

2.1.4 Epidemiology

Osteoarthritis is the most common form of arthritis and generally begins after the age of 40 years. The global prevalence of KOA is estimated to be approximately 3.8% (Vos et al., 2015) and it is estimated that 242 million people being affected by knee or hip OA worldwide.

In epidemiologic studies, OA can be defined radiographically or symptomatically. Radiographic definition considers only pathophysiological joint signs present on radiographic images, while the symptomatic definition considers cases when both radiographic and joint symptoms (pain, stiffness and restricted function). Some epidemiological studies estimate OA prevalence based on self-reported subjective definition of OA where patients were asked if they had any joint pain over the previous year (Thomas et al., 2014).The prevalence of OA and KOA varies according to the definition used within each study, with radiographic definition resulting in generally higher estimates while the symptomatic definition and self-reported estimates present more similar estimates (Pereira et al., 2011).

In the UK, the precise prevalence estimates for OA/KOA remain difficult to find, due to variable definitions. For example, the prevalence of radiographic KOA was measured in 513 subjects with and without painful knee symptoms

using data from a general practice in Bristol. The radiographic prevalence of KOA was found in 53% of the symptomatic subjects and in 17% of asymptomatic subjects (McAlindon et al., 1992).

On the other hand, the prevalence of knee pain was measured in a cross-sectional study using data from general practices in south east quadrant of England between 2001 and 2003. Data were collected through postal questionnaire and 17% of the respondents reported chronic knee pain (n=2,504) (Parsons et al., 2007).

In recent years, primary care electronic Health Records (EHR) are increasingly used to estimate the occurrence of OA. When using databases to find estimates, the prevalence of currently recorded KOA in a general practice in England was 1.1% (Bedson et al., 2005). However, the prevalence estimates also differed with the use of different databases. For example, a study compared the consultation prevalence of musculoskeletal conditions (MSK) using four national data bases. The percentage of recorded OA consultations ranged from 9.4% using the Clinical Practice Research Datalink (CPRD 2001), 9.8% using the Consultation in Primary Care Archive database (CiPCA- 2001) ,11.9% using the Royal College of General Practitioners' weekly returns services (2001) and 19.2% using the fourth morbidity statistics from general practice (MSGP4- 1991/92) (Jordan et al., 2007a).

The current national estimates are based on OA consultation prevalence, that is the number of people aged 45 years and over given a diagnosis of OA, or recorded as having symptom in one of four main joints (knee, hip,

hand, and foot/ankle) in the absence of a record of another diagnosis for these symptoms. A 7-year consultation period was used (2004-2010) to estimate consultation prevalence. This avoided any potential under recording to occur if only annual consultation data were used. It is currently estimated that 8.75 million people aged 45 years and over in the UK, have sought treatment for OA (ArthritisResearchUK, 2013), and that 18.2% of people aged over 45 years in England have KOA , that is 4.11 million people, 1.4 million of whom have severe KOA (VersusArthritis, 2019).

More recently, Yu et al. (2017) estimated the population trends of annual consultation incidence for KOA using CPRD data between 1992 and 2013. The incidence of age and sex standardised KOA remained relatively stable ranging between 3.0 (95%CI 2.9, 3.0) and 1.9 (95%CI 1.8, 1.9) per 1000-person years in 1992 and 2013 respectively (Yu et al., 2017) .

2.1.5 Risk Factors for Osteoarthritis

Several risk factors have been identified and OA/KOA is considered a consequence or the final common pathway for the interaction of systemic and joint specific risk factors. (Table 2-2). A selection from risk factors are further detailed with a focus on KOA where applicable.

Table 2-2 Summary of Risk Factors for OA/KOA

Systemic Risk Factors	**Joint Specific Risk Factors**
Sociodemographic (age and female gender, race/ethnicity)	Biomechanical stressors (occupation or joint injury)
Obesity	Joint malalignment
Genetic disposition	

2.1.5.1 Sociodemographic Factors

Age is one of the strongest risk factors for KOA. The incidence and prevalence of KOA increase with older age as a consequence of cumulative exposure to various risk factors and biologic changes of aging. (Mora et al., 2018). In the UK, it is estimated that within those aged 45 to 64 years, 23% males and 31% females are affected by OA, whereas among those aged 65 to 74 years 35% and 44% are affected respectively and among those aged 75 years or over it is estimated that 42% of males and 49% of females are affected (i.e. number of affected people increase with age) (ArthritisResearchUK, 2013).

Female gender is another risk factor for KOA with females being more affected and burdened by KOA than men. For instance, in the UK, the age standardised incidence estimates of KOA in 2013 were 20.8 (women) and 18.5 (men) per 1000-person years (Yu et al., 2017). Similarly, data reported by the Dutch Institute for Public Health showed a prevalence of 15.5% and 30.5% radiologic KOA in men and women respectively (Bijlsma and Knahr, 2007).

2.1.5.2 Obesity and Metabolic Syndrome

Obesity is associated with KOA as it may increase loading on the joint due to mechanical stress resulting from high body mass index (BMI) in addition to metabolic factors. Obesity is thought to be a part of metabolic syndrome, a syndrome that consists of interrelated factors of metabolic origins such as hypertension, dyslipidaemia and insulin resistance (Georgiev and Angelov,

2019). The risk of developing OA was found to be twice as high in overweight persons compared to those with normal BMI (OR 1.98 95%CI [1.57, 2.20]) and in obese persons the risk was even higher (OR 2.66 95%CI [2.15, 3.28]) (Silverwood et al., 2015).

2.1.5.3 Biomechanical Stressors

Biomechanical stressors, such as heavy physical workload, long hours of kneeling or squatting, long standing (>2 hours/day), heavy lifting (>10 kg) and repetitive movements were also found to contribute to a higher risk of OA. Occupations (e.g. construction, farming, mining, firefighting, hotel room cleaning, food processing and dentistry) involving abnormal or excessive lower extremity joint loading are associated with hip and knee OA (Yucesoy et al., 2015). Joint trauma or injury to the structures of the joint is also an important risk factor particularly for KOA (Silverwood et al., 2015).

2.1.6 The Impact of Osteoarthritis

Osteoarthritis incurs a substantial economic burden, due to its effect on labour market and health care resource use (ArthritisResearchUK, 2013).

Data on the impact of OA are included within the overall impact of the musculoskeletal (MSK) conditions. Musculoskeletal conditions are the leading cause of disability in adults in the UK and remained the leading cause of years lived with disability (YLDs) in the UK in both 2010 and 2015 with a 5% increase over this time. It was reported that OA of the knee accounts for 83% of the total OA burden (James et al., 2018).

MSK conditions were the second most common reason for sickness absence in the UK labour market accounting for 27.8 million days in 2018 (ONS, 2019b). This represented 17.9% of total days lost to sickness in 2018 costing the economy £2.85 billion a year with an estimated rise to 3.43 billion a year by 2030 (Versus Arthritis, 2019 , ONS, 2019b).

Osteoarthritis has a larger indirect economic impact than many other conditions, due to its significant effects on rates of absenteeism, reduced levels of productivity at work and the probability of early departure from workforce.

Apart from the indirect economic burden, there are direct health care costs of OA management arising from treatment in primary or secondary care settings. These costs typically consist of costs of consultations, treatments (including analgesics and joint replacement surgeries), hospitalisation and costs of side effects from treatments (Chen et al., 2012). In the UK, OA is primarily managed in general practice, accounting for more than one million general practice consultations every year (Helliwell et al., 2014). In England, 20% of total GP consultations in primary care in a year were for MSK conditions resulting in a huge burden on primary care resources. A surgery consultation in primary care costed £28 in 2017-2018 (Beecham, 2018). Although this burden is exerted by musculoskeletal conditions as a group, nevertheless, OA consists a large proportion of the MSK conditions.

The cost of analgesic use in primary care in England was estimated at £8.5 million between 2005 and 2006 and that of oral NSAIDs was £25 million. By 2010, the cost had increased to £19.2 million and £25.65 respectively

(NICE, 2014a). Data from the prescribing cost analysis (PCA) in England, showed an increase in the Net Ingredient cost (NIC) of opioid analgesics from £212,354,827 in 2008 to £239,502,560 in 2018. However, the proportion of opioids dispensed for CNCP in general and for musculoskeletal conditions specifically is not known. (NHS, 2018). Prescribing cost analysis provides details of the NIC of all prescriptions dispensed in the community in England.

A large proportion of direct cost of OA treatment is due to the cost of joint replacements. The cost of joint replacement accounted for 85% of the total direct treatment cost of £1 billion. There were 120,581 knee replacements (primary and secondary) carried out in the UK in 2017, with KOA being the primary cause for 98% of them in 2017 (NJR, 2018). The overall cost, with the cost of care and management of osteoarthritis and rheumatoid arthritis was calculated as £10.2 billion in the NHS and social care system in 2017 (VersusArthritis, 2019).

At the individual level, pain and disability caused by OA have a direct impact on individual patient's well-being and result in a substantial loss in quality of life (Conaghan et al., 2015a). Patients with OA report compromised ability to perform the basic activities of daily living (e.g. changing from siting to standing position) and 81% of people with OA in the UK experience constant pain (Conaghan et al., 2015b)(James et al., 2018).

2.1.7 Pain Mechanisms Involved in OA/KOA

Pain is a hallmark symptom of OA and it is generally considered nociceptive resulting from joint tissue destruction. However, recent research has aided the understanding of pain in OA and showed that prolonged pain can result in changes in the central nervous system (CNS) causing a state of central sensitisation. Both peripheral and central neurophysiological mechanisms contribute to the pain of OA. Pain may result from nociceptors of the deep somatic tissue local to the knee becoming sensitised during inflammation. Neurons from the inflamed joints become hyper excitable resulting in amplification of painful sensation (peripheral hyperalgesia). Additionally, the excitation threshold is lowered with an increased response even to non-noxious stimuli (allodynia). This phenomenon is known as neuroplasticity and arises when neurons become sensitive and respond more profoundly to stimuli and become more connected to the neurons in CNS, thus resulting in central sensitisation (Lluch Girbés et al., 2013). Central sensitisation is defined as an amplification of neural signalling within the CNS that elicits pain hypersensitivity. It happens overtime as a response to continued joint pathology, accompanied by increased response to stimuli from a greater area around the joint resulting in patients reporting pain from an extensive area which may be away from the affected joint. Central sensitisation is a condition of the nervous system that is associated with the development and maintenance of chronic pain (Fingleton et al., 2015). The mechanism of central sensitisation also involved an imbalance of serotonin norepinephrine systems within the central pain pathways, which played an important role in the development of pain sensitisation (Gao et al., 2019).

The understanding of pain mechanisms in OA led to the conclusion that the nature of OA pain progresses from nociceptive to neuropathic (NP) with advancing stages of the disease.(Dimitroulas et al., 2014).

The involvement of NP component in OA related pain was also seen/acknowledged within clinical setting where prescribed analgesics failed to produce the desired analgesia. Observational studies showed that long-term use of standard treatments (paracetamol, NSAIDs and opioids) failed to reduce mean pain level beyond minimal clinically important threshold resulting in impaired QoL (Conaghan et al., 2015a). This was in an observational study of 1,187 patients aged 50 years or over who were diagnosed with KOA and prescribed with topical or oral analgesics (including paracetamol, NSAIDs or opioids), the results found that 54% patients had suboptimal pain relief and continued to experience persistent moderate to severe pain. (Conaghan et al., 2015a).

Research also showed that neuropathy-like symptoms are highly prevalent in patients with clinically severe painful OA. Several studies suggested a NP component within OA pain, including qualitative studies in which participants used descriptions suggesting a NP such as: stabbing and burning pain (Hawker et al., 2008, Hochman et al., 2010, Hochman et al., 2011, Valdes et al., 2014).

Several Randomised Controlled Trials (RCTs) evaluated the efficacy and safety of duloxetine, an antidepressant within the selective serotonin norepinephrine reuptake inhibitor (SNRI) class. A systematic review of five

RCTs showed that compared to placebo, treatment with duloxetine showed reductions in pain intensity (mean difference [MD] =-0.77, p<0.0001), higher reduction in pain severity (risk ratio [RR] 1.42, P<0.0001), lower mean patient Global Improvement Inventory (PGI-I) score (MD=-0.48, P<0.0001) (Gao et al., 2019). Duloxetine has been recommended by the Osteoarthritis Research Society International (OARSI) guidelines for the management of KOA as a therapeutic option when NSAIDs are inappropriate/contraindicated (McAlindon et al., 2014, Bannuru et al., 2019). The role of duloxetine was also acknowledged by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), and it was included in their algorithm on the management of KOA (Bruyère et al., 2014).

In the UK, the initial treatment of neuropathic pain in non-specialist setting as recommended by the NICE guideline includes prescribing antidepressants or anti-epileptic drugs (AEDs). The recommended specific antidepressants include the tricyclic antidepressants (TCAs) specifically amitriptyline and serotonin norepinephrine reuptake inhibitors (SNRI) specifically duloxetine. The recommended AEDs include pregabalin and gabapentin (NICE, 2013b).

2.1.8 Management of Osteoarthritis

Management strategies for OA generally include non-pharmacological and pharmacological aspects and the overall aims are to control pain and restore

joint function. Both aspects are often applied for optimal management, depending on individual patient's pain severity and treatment goals.

To standardise and recommend the available treatment options, several evidence-based treatment guidelines have been developed by multiple academic and professional societies. Among these are the UK National Institute for Health and Care Excellence (NICE), the European League against Rheumatism (EULAR) and the OARSI guidelines. This section provides a brief overview of the management recommendations, with a focus on NICE recommendations.

Surgical interventions (e.g. knee arthroplasty) are recommended when the non-pharmacological and pharmacological treatments have failed to provide adequate pain control.

2.1.8.1 Non-Pharmacological Management

Clinical guidelines universally recommend patient education and self-management, exercise and weight reduction for overweight and obese patients as the starting steps of management. The NICE guideline indeed refers to these recommendations as core treatments that need to be offered to all people with clinical OA, regardless of age, pain severity and comorbidities (NICE, 2014b). It also recommends a set of treatments as adjuncts to core treatments including thermotherapy (local use of heat or cold), electrotherapy (transcutaneous electrical nerve stimulation [TENS], bracing/joint supports/insoles and assistive devices (e.g. walking sticks).

Recent research has shown that exercise and physical therapy enhance mobility and reduce pain and increase patients' self-management. Light physical activity provides mechanical and functional improvements; it slows cartilage degeneration resulting from its softening and thinning. Exercise routines also offer a risk reduction of diabetes, cardiovascular events as well as an improvement in mood (Esser and Bailey, 2011, Bennell and Hinman, 2011).

There are different land-based exercises including aerobic, stretching, resistance or balance exercises that can be tailored to individual needs. In addition, aquatic exercises (water based) have shown to have favourable affect in KOA (Tanaka et al., 2013). A recent Cochrane meta-analysis including 44 studies showed that compared to those who did not exercise, patients with KOA who performed exercise programs had a reduction in pain by 12 points (95%CI 10, 15) on a scale of 0 to 100. Exercise also improved physical function by 10 points (95%CI 8, 13) on a scale of 0 to 100 and this effect was sustained for 2 to 6 months after stopping the exercise (Fransen et al., 2015).

Weight reduction plays an important role in the management of patients with KOA. A significant dose response relationship was reported between the percentage change of body weight and the extent of change in the physical function and pain score measured by the Western Ontario McMaster universities index (WOMAC) for physical function and pain scales. Those who gained 10% of body weight or more, had WOMAC physical function score changes of -5.4 points (95%CI -8.7, -2,0) indicating worsening

compared to reference group (persons with weight changes of between <5% weight gain and <5% weight reduction) (Riddle and Stratford, 2013).

NICE recommends offering advice on interventions to achieve weight loss as a core treatment to obese or overweight people (NICE, 2014b).
Additional non-pharmacological management approaches include complementary and alternative medicines (e.g. nutritional supplements, massage and acupuncture) have been studied, however, the evidence supporting their use is still unclear, thus were not recommended by NICE (NICE, 2014b).

2.1.8.2 Pharmacological Management

Pharmacological management includes the use of systemic and topical analgesics including paracetamol, topical and oral NSAIDs and opioids applied in a sequential hierarchical approach to provide stepwise analgesia. There is a consensus on the overall pharmacological recommendations among the OA treatment guidelines.
Paracetamol is widely prescribed in primary care for musculoskeletal pain, however, evidence showed modest efficacy compared to placebo in patients with knee or hip OA. A systematic review including 10 RCTs was conducted to investigate the efficacy and safety of paracetamol vs placebo in the management of OA (Machado et al., 2015). Paracetamol use for longer than 2 weeks and less than 3 months, provided a statistically significant but clinically not important effect on pain and disability (weighted

mean difference of -3.7 (95%CI -5.5, -1.9) and -2.9 (95%CI -4.9, 0.9) respectively. (Machado et al., 2015).

These results were confirmed by a recent Cochrane review (update of the review of Machado 2015) which showed that paracetamol provided only minimal improvements in pain and function compared to placebo in patients with hip or knee OA. Pain improved by 3.2 points (95% CI 1.0, 5.4) and physical function improved by 2.9 points (95%CI 1.0, 4.9) with paracetamol use (Leopoldino et al., 2019). A subgroup analysis of paracetamol dose was performed to compare lower and higher dose (3.0 g/day or less versus 3.9 g/day or more). There were no important differences in outcomes for low dose versus high dose with regard to pain or physical function (Leopoldino et al., 2019). Consequently, the OARSI guideline did not recommend paracetamol for any OA phenotype or any comorbidity subgroup in its last update in 2019 (Bannuru et al., 2019), whereas, it is still recommended by NICE (NICE, 2014).

Topical NSAIDs were shown to be superior to placebo for pain control and function improvement in a recent meta-analysis including 36 RCTs (Zeng et al., 2018). Topical diclofenac was found to be most effective among the studied topical NSAIDs for relieving pain, with a standardised mean difference in effect sizes (SMD) of -0.81, (95%CI -1.12, -0.52). Piroxicam was most effective for functional improvement with SMD= -1.04 (95%CI -1.60, -0.48) compared with placebo (Zeng et al., 2018). Hence, topical NSAIDs offer an alternative to decrease the risks of systemic NSAIDs.

The clinical guideline by NICE recommends topical NSAIDs ahead of any systemic analgesic including paracetamol, oral NSAIDs and opioids (NICE,

2014b). Similarly, the clinical guideline by OARSI strongly recommends topical NSAIDs (Bannuru et al., 2019), and EULAR endorses their clinical efficacy and recommends topical NSAIDs and/or capsaicin (Jordan et al., 2003).

The use of oral NSAIDs is recommended by most treatment guidelines, however, detailed attention must be devoted to the assessment of risk factors for developing adverse reactions related to NSAIDs. A network meta-analysis was conducted to assess the effectiveness of different preparations and doses of NSAIDs on knee and hip OA pain and physical function (da Costa et al., 2017). It was reported that diclofenac 150mg/day was the most effective NSAID for pain control and physical function, however, the authors have advised that the safety profile should be taken into consideration.

The use of opioids has emerged as a treatment option that may provide effective pain relief with less risk than NSAIDs. However, evidence to support using opioids in OA is rather limited (da Costa et al., 2014). Traditionally, opioids were used for acute pain and in palliative care settings; however long-term opioids use in patients with OA is controversial due to the lack of sufficient evidence for supporting the effectiveness of their long-term use (Chou et al., 2009). A large Cochrane systematic review showed that opioids had only a small effect on pain and of questionable clinical relevance (da Costa et al., 2014). Recently, a pragmatic trial including 240 patients was conducted to compare opioid vs non-opioid medications over 12 months on pain-related function, pain intensity and adverse effects in patients with low back pain or hip and knee OA. Results showed that there

was no significant difference in pain-related function between the opioid group and non-opioid group (consisted of step wise administration of paracetamol, NSAIDs, antidepressants or AEDs) (Krebs et al., 2018). At 12 months, mean Brief Pain Inventory (BPI) interference scale was 3.4 (SD 2.5) in the opioid group vs 3.3 (SD 2.6); difference of 0.1 (95% CI -0.5, 0.7). The BPI was a 10 points scale (higher score means worse function) and the minimal clinically important difference was set at a 1-point difference for BPI interference between opioid and non-opioid groups. The authors concluded that the trial results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

Surgical interventions such as Total Knee Arthroplasty (TKA) are indicated for advanced OA non-responsive to the pharmacological and non-pharmacological.

2.2 Safety of Analgesics Recommended by OA Treatment Guidelines

Osteoarthritis is a chronic condition for which treatments are prescribed for prolonged periods, hence safety is crucial. Paracetamol is recommended as a first step analgesic by most OA treatment guidelines. However, the safety of paracetamol has been questioned in several studies; evidence suggested an association between gastrointestinal (García Rodríguez and Hernández-Díaz, 2004, Garcia Rodríguez and Hernández-Díaz, 2001), cardiovascular (Chan Andrew et al., 2006) and renal toxicities (Curhan et al., 2004). This along with the minimal pain and joint function improvements, have called for further research investigation of the role of paracetamol as a first line

therapy in many clinical practice guidelines (Roberts et al., 2016, Conaghan et al., 2019b).

NSAIDs carry a heightened risk of cardiovascular adverse events, renal failure and gastrointestinal bleeding (Crofford, 2013). The risks of these adverse effects vary according to the mechanism of action of the individual NSAID. Selective Cyclooxygenase-2 (COX-2) inhibitors were found in several RCTs to be associated with a greater cardiovascular risk including myocardial infarction, heart failure and stroke. For example, a trial including 2,586 patients who underwent randomisation to receive 25mg rofecoxib (COX-2 inhibitor) and placebo. There were 1.5 cardiovascular events per 100 patients-years in the rofecoxib group compared to 0.78 events in the placebo group, and the corresponding relative risk (RR) was 1.92 (95% CI 1.19,3.11) p=0.008 (Bresalier et al., 2005). Subsequently, and as further evidence emerged, rofecoxib was withdrawn from the market in 2005 (Bresalier et al., 2005).

Gastrointestinal adverse effects include dyspepsia, esophagitis, GI ulcers, ulcer complications (bleeding, perforation) and colitis. Additionally, the renal adverse effects include hypertension, acute renal failure, acute interstitial nephritis and accelerated chronic kidney disease (Bresalier et al., 2005). Evidence showed that the non-selective NSAIDs are more likely to produce GI related adverse effects compared to COX-2 inhibitors (Crofford et al., 2004).

Immediate adverse effects of opioids (occur close after initiation) include constipation, nausea, vomiting, pruritus, sleep disturbances, cognitive

impairment, dizziness, somnolence and sedation (Rogers et al., 2013, Papaleontiou et al., 2010). The use of opioids was associated with risks of falls and fractures which is a serious potential consequence of falling (Saunders et al., 2010, Li et al., 2013).

A cohort study reported a significantly increased risk of fracture among patients with CNCP who used opioids for chronic pain (≥ 3 prescriptions within the first 90 days of an episode of opioid use). Opioid users were at twice the risk of fracture compared to non-users, HR 2.0 (95%CI 1.24, 3.24) with doses oral morphine ≥ 50 mg/day (Saunders et al., 2010). However, the potential mechanism behind the risk was not clear, and it was not known whether opioid induced hypogonadism was the plausible mechanism or was it the acute CNS effect (sedation and dizziness).

This question was addressed in a nested case control study using CPRD data selected adult cases with first diagnosis of fracture of the hip, humerus and wrists. Opioid use within a year of fracture was specified and the risk of fracture was compared between users and non-users. Current opioid use was associated with a significantly greater risk of fracture compared to non-users with OR of 1.27 (95%CI 1.21, 1.33) adjusted for comorbidities, concomitant medications and smoking. The study found that compared with nonusers, current opioid users who had received one prescription had a greater risk of fall, with an adjusted OR of 2.70 (95%CI 2.34, 3.13) compared to non-users. The risk decreased with increasing use and those using 6-20 prescriptions, the OR was 1.17 (95%CI 1.08,1.27) (Li et al., 2013).

The above findings led to the conclusion that the risk of fracture was associated with the acute CNS effects of opioids (e.g. sedation and

dizziness) which were risk factors for falls. This was an important finding in the context of the dramatic increase in opioid utilisation reported in several studies in the UK (Zin et al., 2014).

Adverse events with antidepressants reported in observational studies included insomnia, sleepiness during the day, restlessness, muscle spasms/twitching, dry mouth, profuse sweating, sexual disorders, nausea, constipation, diarrhoea, weight gain and dizziness (Bet et al., 2013). While common adverse effects of AEDs include drowsiness, fatigue, dizziness, blurred vision and incoordination (St Louis, 2009).

From the above overview on safety of OA treatments, it is observed that acute CNS effects such as sedation, dizziness were common adverse effects of most of the analgesics used by patients with KOA, which were risk factors for a serious adverse event such as falls. However, the association between analgesic use and the risk of fall in patients with KOA is not well described. Patients with KOA may be using several analgesics simultaneously (Wilson et al., 2015), however, it is not clear whether the risk of fall differs among patients prescribed multiple analgesic classes compared to those prescribed a single class. This leads onto the rationale for selection of falls as the outcome of interest in this research.

2.3 Rationale for Selection of Fall as the Clinical Outcome of Interest

The rationale for selection of falls as the clinical outcome of interest within this study was informed by the burden of falls in the UK and the paucity of

data on the association between analgesic use and the risk of fall in patients with KOA, as detailed in the following sections.

2.3.1 Scale of the Problem in General Population

Falls represent a major public health challenge in the UK and many other countries worldwide; with as many as 30% of older people (aged 65 years or older) having a fall at least once every year (WHO, 2007). A fall is defined by the World Health Organisation (WHO) as “inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects” (WHO, 2007).

Although falls cause moderate to severe injuries, the psychological impact of falling can be devastating. Even ‘minor’ falls can be very debilitating, individuals can lose confidence and become anxious about falling again. This means they may become unwilling to move about, and as a result become more isolated and more dependent on others. Consequently, this leads to a greater burden on carers, and an increased likelihood that an individual will need residential care.

In the UK, the financial impacts on NHS and social care are substantial, incurring the use of GP visits, ambulance journeys and community care. Additionally, falls are the leading cause of injury-related hospitalisation and increase the burden on hospital services; both accident and emergency (A&E) visits as well as inpatient admissions. Falls and fractures among those aged over 65 years take up 4 million hospital bed days each year in England, costing up to £2 billion (NHS, 2012). The Public Health

Outcomes Framework (PHOF) reported that in 2017 to 2018, there were 220,160 emergency hospital admissions related to falls among patients aged 65 years and over (PHE, 2019b). Falls were the ninth highest cause of disability-adjusted life years (DALYs) in England in 2013 and the leading cause of injury (PHE, 2019a).

2.3.2 Overview of Risk Factors for Falls

Epidemiologic studies have identified a number of risk factors for falls including sociodemographic, lifestyle, clinical conditions, environmental, psychological and medication use. Examples of each of these factors are summarised in Table (2-3). (Kannus et al., 2005).

Table 2-3 Risk Factors for Falls and Examples

Risk Factor	Examples
Sociodemographic	Advanced age, female sex, ethnicity/race, living alone
Lifestyle	Inactivity, use of walking aids
Clinical conditions	Postural instability, sensory and neuromuscular function, impaired cognition, stroke, depression, orthostatic hypotension, vestibular disorders
Environmental	Poor footwear, inappropriate spectacles
Psychological	Fear of falling
Medication use	Cardiovascular, central nervous system medications

Falls result from a complex interaction of risk factors and are common in older aged people (≥65 years) as a result of several physiological changes. Age-related physiological changes in cardiovascular reflexes can result in orthostatic hypotension which can predispose to falls. Additionally, other age-related changes such as visual and vestibular impairments, hearing loss, reduced postural control, slowing of gait speed and a decrease in lower

limb strength all contribute to the increased risk of falls (Lavan and Gallagher, 2016).

2.3.3 Additional Risk Factors for Falls in Patients with OA/KOA

In common with the older population, several age-related pathophysiological changes are seen in patients with OA/KOA. Additionally, KOA itself has been identified as a risk factor for falls, due to knee joint instability and muscle weakness (Manlapaz et al., 2019). Moreover, the presence of severe knee pain was also associated with an increased risk for fall in patients with KOA as reported in a study from England and Wales in which patients with severe pain were at a greater risk for fall compared to those without severe pain, HR (95%CI) 1.5 (1.32-1.75) (Arden et al., 2006).

In addition to the physiological and pathological factors contributing to the risk of fall, the use of analgesics is common among patients with KOA, ranging from 50% to 64% in community dwelling patients with OA (Gore et al., 2012, Wilson et al., 2015, Wright et al., 2014). Analgesic use was shown to be associated with an increased risk of falls; however, the evidence is not conclusive as discussed subsequently (section 2.3.4).

2.3.4 Current Knowledge on Medication Use and Risk for Falls

Medication use is a particularly important and has been investigated as a risk factor for falls in older adults in a large number of studies. Commonly studied drug classes included cardiovascular drugs, different types of

psychotropic drugs such as sedatives, hypnotics, antipsychotics, benzodiazepines, antidepressants and antiepileptic drugs (AEDs) in addition to analgesics such as NSAIDs and opioids. Several plausible mechanisms are implicated by which various medications affect the balance system including reduced level of mental alertness, impaired transmission within the central nervous system (CNS), sedation, confusion and reduced neuromuscular coordination and balance. The role of certain medication classes (e.g. benzodiazepines), and the risk of falls is well established however, the evidence for the role of some other classes (e.g. opioids and NSAIDs) is inconsistent.

Evidence on the possible role of medication use and falls is generated mostly from observational studies. A summary of key studies that have informed the evidence on the association between medication use and the risk of falls is presented in Table (2-4). The included studies were those that were conducted in general community dwelling older adults and/or in patients with OA or KOA specifically. The table is followed by a commentary on the methodology of included studies.

Table 2-4 Summary of Studies on Medication Use and Risk for Falls in Community Dwelling Adults

Author, Year, Country	Population (age Inclusion Criteria) and Setting	Study Design	Number of Patients	Exposure	Method of Fall Detection	Result	Limitation
ANALGESICS							
Leveille 2002 USA	community-dwelling, women, musculoskeletal pain aged ≥65years	Prospective cohort study	940	Baseline	Falls in 3-year follow-up, recall (6 months)	OR (95%CI) 0.79 (0.63–0.98)	No information on confounders Population of disabled women
Lawlor 2003 UK	community-dwelling, women mean age: Fallers 70.1 years Non-fallers 68.6 years (range 60-79)	cross-sectional	4,050	Analgesic use was assessed through an interview	Fall and recurrent fall in past 12 months, recall (12 months)	OR (95%CI) Fall 1.00 (0.79 - 1.25) Recurrent fall 1.20 (0.87 - 1.65)	Included women only
Larsen, 2004 Danemark	community-dwelling ≥66 years (range 66-106)	cross-sectional	4,281	At fall	Fall in past 24 hours, recall (1day)	OR (95%CI) Female 2.20 (1.11 – 4.36) Male 1.91 (0.46 – 6.38)	
French 2006	National Veterans Health Administration (VHA) ≥66 years with One fall related outpatient encounter in 2004	Cross sectional	20,551	Prescription of CNS medications including Antidepressants AEDs Opioids	Diagnostic codes within calendar year 2004	More patients with a fall coded encounter used CNS drugs than the controls 42.05%vs.29.29% (p<0.02)	Inadequate control of confounders
Hanlon, 2009 USA	70-79 years old Residing in specific zip code Enrolled between 1997-98 in the Health ABC study and followed up for 5 years	Longitudinal cohort study	3,075	Exposure to opioids and antidepressants measured at baseline and annually for 4 years. Medication use was ascertained by an interview. Exposure was quantified as the number of medications used (1 or+2)	Self-reported recurrent fall at 12 months after med use. (12mo)	OR (95%CI) 1.95 (135-2.81) for the use of multiple CNS medications compared with never users	Exposure to multiple drugs was quantified as the number of analgesic classes used, not on the particular classes used

Author, Year, Country	Population (age Inclusion Criteria) and Setting	Study Design	Number of Patients	Exposure	Method of Fall Detection	Result	Limitation
Solomon, 2010 USA	Medicare beneficiaries who qualify for pharmaceutical assistance program for low-income older adults between 1999 and 2005 who had a diagnosis of OA or RA Mean age 80years	Retrospectiv e cohort study	12, 840	Pharmacy dispensing claims records of NSAIDs COX-2 inhibitors Opioids Exposed from one day after dispensing until 15 days after the last available dose.	Claim data diagnoses codes	OR 0.73 (0.47-1.14) for COX-2 inhibitors OR 1.64 (1.09-2.47) for opioids NSAIDs reference	Excluded patients who were dispensed analgesics from 2 categories simultaneously Predominantly very old females in the cohort (85%)
Lo-Ciganic, 2017 USA	Participants of the osteoarthritis initiative study who were diagnosed with KOA or were at risk of developing KOA 45-79 at baseline	Longitudinal analysis	4,231	Self-reported analgesic use within 30 days prior to an annual assessment clinic visit 4 years follow-up	Recurrent Falls within the past year Self-reported Retrospectively collected Recall (12 months)	RR (95%CI) For opioids: 1.22 (1.04-1.45) For antidepressants: 1.25 (1.10-1.41)	Exposure and outcome were self-reported Potential risk for Confounding by indication (participants were from a trial)
Bedson 2019 UK	Patients with MSK conditions identified in CPRD, starting a new episode of long-term opioids between 2002 and 2012 Median age 61 years (IQR 47,73)	Cohort study design	98,140	Prescriptions of long-term opioids (defined as ≥3 prescriptions within 90 days)	Read codes	HR (95% CI) 1.23 (1.19-1.28)	Focused on long term use of a single analgesic class (opioids)
Rolita, 2013 USA	Electronic medical records of patients with OA between 2001 and 2009 age range 65 to 89 years	nested case-control study	13,354	Prescription of opioids or NSAIDs	Diagnoses of falls and fractures were identified according to ICD-9 codes	OR (95%CI) For opioids 3.3 (2.5-4.3) For NSAIDs 4.1(3.7-4.5)	data did not capture the possible influence of concurrent FRIDs

Author, Year, Country	Population (age Inclusion Criteria) and Setting	Study Design	Number of Patients	Exposure	Method of Fall Detection	Result	Limitation
Krebs,2016 USA	Osteoporotic fracture in men study Participants with musculoskeletal pain ≥65 years	Cross sectional	2,902	Self-reported daily or near daily use of opioids at baseline and at 2 additional visits	Self-reported (sent a questioner every 4 months to report fall events)	Risk of fall did not differ significantly RR 1.10 (95%CI 0.99-1.24)	Only men were included Outcome was self-reported every 4 months
Du, 2017 Germany	≥65-year-old Part of the National health Interview and Examination Survey for adults 2008-2011	Prospective cohort	1,833	Analgesics use in the past 7 days prior to the medical interview.	Self-reported during interview	OR (95%CI) 2.66(1.50-4.73)	Although verified with original packaging, fall was self-reported
ANTIDEPRESSANTS							
Coupland, 2011 UK	Older patients (65 to 100 years) with a diagnosis of depression between 1996 and 2007 and followed up until 31st Dec 2008 using data from Q Research	Retrospective cohort study (Population based Database study)	55,767	Antidepressant prescriptions	Read codes for falls extracted from the database	HR (95%CI) TCA 1.30 (1.23-1.38) SSRI 1.66 (1.58-1.73) Other 1.39 (1.28-1.52)	Depression diagnosis but may not necessarily include patients with painful conditions, Confounding by indication
Ensured, 2002 USA	Women ≥65 years	Prospective cohort study with 1 year follow-up	8,127	Current use of antidepressants was assessed with an interviewer-administered questionnaire with verification of use from medication containers.	Incident falls and frequent falls reported every 4 months for 1 year Recall (4mo)	OR (95%CI) For fall 1.22 (0.97-1.53) risk of frequent falls 1.54 (1.14-2.07)	population of females only Medication use and fall were self-reported Risk of recall bias

Author, Year, Country	Population (age Inclusion Criteria) and Setting	Study Design	Number of Patients	Exposure	Method of Fall Detection	Result	Limitation
ANTIEPILEPTICS (AEDs)							
Ensured, 2002 US	Women ≥65 years	Prospective cohort study with 1 year follow-up	8,127	Current use of AEDs was assessed with an interviewer-administered questionnaire with verification of use from medication containers.	Incident falls Reported every 4 months for 1 year. Recall (4mo)	OR (95%CI) For fall 1.02 (0.79-1.31) For frequent falling 0.99 (0.68-1.43)	Population restricted to women Risk of recall bias
Ham, 2014 Netherland	B-proof trial participants Community dwelling elderly aged ≥65 year	Prospective	2,407	Dispensed AEDs captured through Pharmacy dispensing records	Incident of fall on a weekly calendar	HR (95% CI) 1.31 (0.87–1.98)	Fall self-reported on weekly basis

OR odds ratio HR hazards ratio CI confidence interval TCA tricyclic antidepressants SSRIs selective serotonin reuptake inhibitors

2.4 Commentary on the Methodologies of the Above Studies

The above studies have informed the evidence on the association of medication use and the risk of fall however, they may not necessarily inform the risk in patients with KOA. There are several reasons that make them relevant only to a certain degree to patients with KOA.

The minimum age for inclusion in all the above studies was 60 years. Given that KOA begins after the age of 40 years, it is expected that there will be a proportion of younger patients (aged <60 years) among a cohort of people with KOA. This may result in different risk estimates than those reported by the above studies.

Additionally, included patients consisted only of men or only of women or included patients with diagnosed depression for which antidepressants were prescribed (Masud et al., 2013, Ensrud et al., 2002, Coupland et al., 2011). For example, Krebs at al. (2016) in a prospective longitudinal cohort study including 2,902 participants with a mean follow-up period of 9.1 (SD 4.0) years, found no significant difference in the adjusted risk of falling between opioid-use and non-use (HR 1.10, 95% CI 0.99, 1.24) (Krebs et al., 2016). Despite the large sample size and prospective study design, findings from Krebs' study may not be generalizable because the study population consisted of only men and a potential of recall bias as fall ascertainment was only every four months (Table 2-4). These inclusion criteria may have potentially resulted in selection of cohorts which are different than a cohort with KOA, hence findings on the magnitude and significance of the risk of fall may not be generalizable to patients with KOA. Hence, the estimated fall

risks may be different from the risk in patients with KOA, owing to the difference in antidepressants indications and prescribed doses.

Furthermore, the approach to exposure and outcome ascertainment medication had the potential of recall bias. Medication use as well as falls were self-reported during interviews set at specific points in time i.e. at regular intervals ranging from 1 day to 24 months. Although the interview schedules were carefully selected to minimize the potential recall bias, this bias could not be eliminated.

In the majority of the above studies, the use of each analgesic class was separately investigated. For example, Krebs et al. (2016), and Bedson et al. (2019), investigated the association between opioid use and the risk of fall, while patients with KOA were reported to use multiple analgesics (Wilson et al., 2014). The use of multiple analgesics has not been adequately studied. For example, Hanlon et al. (2009) conducted a longitudinal study including 3,055 patients and examined the risk of multiple central nervous system (CNS) medication use for recurrent falls (Hanlon et al., 2009). The use of benzodiazepines, opioids, antipsychotics and antidepressants at baseline, years 1, 2, 3 and 5 had always preceded the ascertainment of falls in the subsequent year. Results showed that over 5 years of follow-up; multiple medication users (2+ classes) were at a greater risk for fall compared to those who did not use multiple CNS medications, adjusted OR (95%CI) 1.95 (1.36-2.81). In this study, fall was self-reported during annual visits, which may have underestimated rates as a result of potential recall bias. Furthermore, the study reported the number of CNS medications used but

details on the types of drug classes defining multiple drug use were not provided. Risk for fall may potentially differ with different combinations of multiple classes (Hanlon et al., 2009). Lo-Ciganic et al. (2017) grouped patients into six mutually exclusive groups based on analgesic CNS potency, for instance, the first group included patients using opioids with or without antidepressants, NSAIDs or nutraceuticals. With this grouping, it is not known whether the associated risk of fall is with the use of all prescribed classes within the group or the risk is only associated with the highest CNS potency (Lo-Ciganic et al., 2017).

Moreover, only a limited number of studies had investigated the association between analgesic use and the risk of fall specifically in the population of patients with OA/KOA (Lo-Ciganic et al., 2017, Rolita et al., 2013) and both studies were conducted in settings outside the UK. There is still a gap of knowledge on the risk for fall in patients with KOA who use more than one analgesic class including (antidepressants, AEDs, opioids and non-opioid analgesics) in the UK.

Population-based epidemiological studies on the association between analgesic use and the risk of fall in UK patients with KOA are limited. Furthermore, the prevalence of use of multiple analgesic classes and its association with risk for falls has not been adequately described in the UK. Investigation and accurate estimation of the risk of fall associated with the use of commonly prescribed analgesics in patients with KOA is essential for developing effective fall-prevention and intervention strategies.

2.5 Drug Utilisation Research

Drug utilisation research is defined by the WHO as “studies on the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences” (WHO, 2003). Subsequently, a group of experts from the International Society of Pharmacoepidemiology (ISPE) defined drug utilisation research as “an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes” (Wettermark et al., 2016) . Both definitions have linked drug utilisation research to the field of pharmacoepidemiology which applies epidemiological methods to clinical studies on drugs in populations.

Drug utilisation studies can be divided into descriptive and analytical. Descriptive studies describe patterns of drug utilisation while the analytical studies link drug use to morbidity, outcome of treatment and quality. Drug utilisation research is thus an essential part of pharmacoepidemiology as it described extent and determinants of drug exposure. Over time, the distinction between the two terms is less visible and they are used interchangeably sometimes.(WHO, 2003).

2.5.1 Importance of Drug Utilisation Research

Drug utilisation research and pharmacoepidemiology increase our understanding of how drugs are being used and provide important insights

on patterns on drug use through estimating the numbers of all patients exposed to specific drugs within a given time period (prevalence of use) or focus on new users (incidence of use). Such description is most meaningful when trends are described over time and compared across drug and drug classes producing a comprehensive picture of the population's drug use and its dynamics.

Several data sources can be sought for drug utilisation information such as aggregate data on drug consumption or use data from regulatory agencies within a country, however, the availability of electronic Health Records (EHRs) in recent years provided an opportunity for drug utilisation/ pharmacoepidemiologic studies. EHRs, whether collected as routine medical records or for administrative purposes, are extensively used for studies on prescribing trends, adverse drug effects and risk management, beneficial drug effects and health policy research (Schneeweiss and Avorn, 2005). For example, data from The Health Information Network (THIN), a UK primary care database were used to study the association between the use of venlafaxine and the risk of fall in the UK (Gribbin et al., 2011). However, EHRs differ across countries in their population representativeness and the breadth of detail of information they contain, their data quality and linkability with data from other sources (e.g. cancer registries) (Wettermark et al., 2016).

2.5.2 Drug Utilisation Research in Patients with OA/KOA

Drug utilisation studies in patients with OA/KOA was the focus of several national and international studies. A literature search was performed to find all relevant studies in which the primary objective was to investigate the utilisation of drugs in patients with OA/KOA identified through EHRs.

Several studies were identified, including those focusing on a single class or multiple analgesic classes, or applied cross-sectional or cohort study designs and were conducted in the UK or other countries. The studies are summarised in Table (2-5), followed by a commentary on their methodology.

Table 2-5 Summary of Drug Utilisation Studies in Patients with OA/KOA Using EHRs

Author, Year, Country	Data Source	Study Design/ Number of Patients	Drug Class(s),	Main Findings	Limitation
Gore, 2011 USA	The LifeLink™ Health Plan Claims Database	Cohort study of 112,951 diagnosed with KOA 64,085 received a prescription	Paracetamol NSAIDs Opioids Antidepressants	Opioids were used by 71.7% NSAIDs by 65.4% Tramadol by 17.3% Paracetamol by 2.0% Antidepressants by 32.0%	Confined to specific calendar year 2008, not over time.
Gore, 2012 UK	The Health Improvement Network (THIN)	Cohort study over one year of respective drug initiation	NSAID Opioids	discontinuation rate ranged between 84-93% proportion who switched to other treatment within the first 2 months of initiation was 30-60% Augmentation rates were from 8.7% to 15%.	Excluded patients with OA who were prescribed more than drug on the index prescription
Kingsbury, 2013 USA	Osteoarthritis Initiative (OAI) database, a publicly available multi-centre population-based observational cohort study of knee OA	Cross sectional and longitudinal study over 36 months 987 subjects	Paracetamol NSAIDs Opioids Nutraceutical	NSAIDs were the most frequently prescribed class (26.8%) Opioids were only used by a small number of patients (3.3%).	Included those with symptoms plus radiographic evidence of KOA Medication use was self-reported
Wright, 2014 USA	the Medicare Current Beneficiary Survey (MCBS) The KOA cohorts were selected from community-dwelling adults	Cross sectional, trends of prescribing in 2003, 2009 and 2009	NSAIDs Opioids	increase in the proportion of patients using opioids from 31% in 2003 to 40% in 2009 (OR 1.5, 95% CI 1.1, 2.0 for 2006 and 2009 compared to 2003) NSAID use decreased from 41% to 31% (p=.0008)	MCBS prescribed medication data are obtained by interviewer-guided patient interview

Author, Year, Country	Data Source	Study Design/ Number of Patients	Drug Class(s),	Main Findings	Limitation
Wilson, 2014 Spain	Sistema de información para el Desarrollo de la investigación en atención Primaria (SIDIAP) database	Cohort study prevalence of medications and nutraceuticals over five years 2006-2010 238,536 patients	topical NSAIDs paracetamol Oral NSAIDs opioids nutraceuticals	The most commonly used drug class was NSAIDs (77.4%) and combination of three drugs classes the most commonly used regimen (53.9%)	Included nutraceuticals, OTC and prescriptions drugs.
Yu, 2017 UK	Clinical Practice Research Datalink (CPRD)	Cross sectional repeated measures of drug use incidence between 1992 and 2013	NSAIDs Opioids	The incidence of strong opioid prescribing increased from	Excluded paracetamol due to potential under estimation as result of access through OTC purchase
Inacio,2018 Australia	The Australian Government Department of Veterans Affairs	A population-based study between 2001-2012 within one-year prior to total knee replacement (TKR) 15,162 patients	Paracetamol, NSAIDs Opioids Neuropathic pain medications (NP): Pregabalin, Gabapentin Amitriptiline	prevalence of opioid use increased from 37% to 49% NP medication increased from 5% to 11% NSAID use decreased from 76% to 50%	Described the use during the year prior to TKR, however, only a small proportion of patients with KOA who use analgesics would be waiting for TKR.
Thorlund, 2018 Sweden	Swedish Prescribed Drug Register (SPDR)	Population-based cohort study. 751,579 patients with diagnosed knee or hip OA	Opioid	The 12-month prevalence of opioid use among OA patients was 23.7% [95% (CI) 23.3-24.2] This was two-fold higher compared to individuals without knee or hip OA: prevalence ratio: 2.1 [95% CI 2.1-2.1].	Focussed only on opioids
Appleyard, 2019 UK	Clinical Practice Research Datalink (CPRD)	1995 to 2015 383,680 patients diagnosed with OA	Gabapentin Pregabalin	35,031 were prescribed at least one prescription annual age-standardised incidence rate of first gabapentinoid prescriptions rose from 1.6 [95% (CI): 1.3, 2.0] per 1000 person-years in 2000, to 27.6 (26.7, 28.4) in 2015	Focussed only on gabapentinoids

Author, Year, Country	Data Source	Study Design/ Number of Patients	Drug Class(s),	Main Findings	Limitation
Akazawa, 2019 Japan	Administrative hospital claim database	Retrospective cohort study 118,996	Opioids NSAIDs Paracetamol Duloxetine Pregabalin	Proportion of patients using respective drug classes: NSAIDs:67.0% COX-2 :48.4% Paracetamol by 21.4% opioids were used by 21.7% Duloxetine by and pregabalin by 1.3%	Only fentanyl was included among the strong opioids Hospital claim database, not representative of primary care patients Data on outcomes (e.g. data on adverse effects) not available

OA osteoarthritis KOA knee osteoarthritis NSAIDs non-steroidal anti-inflammatory drugs NP neuropathic pain CI confidence interval COX-2 cyclo-oxygenase inhibitor OR odds ratio

2.5.3 Commentary on the Methodology of the Above Studies

From the above overview of studies of drug utilisation in patients with KOA, it was observed that a considerable proportion of these studies focussed only on a single drug class e.g. gabapentinoids. (Appleyard et al., 2019). Although important insights were provided on their utilisation, the overall picture on changing trends of other drugs' utilisation over time were not studied simultaneously.

Additionally, even the studies of multiple analgesics in patients with OA/KOA, only a few of them have also included drugs that are used for NP pain (e.g. antidepressants or AEDs such as pregabalin and gabapentin) (Inacio et al., 2018, Akazawa et al., 2019). Antidepressants e.g. amitriptyline and duloxetine and AEDs e.g. pregabalin are recommended for NP pain management, however, the extent of their utilisation in patients with CNCP conditions generally and OA specifically, remains understudied.

Furthermore, drug exposure was obtained from different sources including primary care EHRs (e.g. CPRD in the UK), claims databases (e.g. Lifelink in the USA), however, medication use data were also obtained through patient interview such as in the study by Wright et al, (2014), which can form a source of recall bias. Whereas in the study by Akazawa et al. (2019), administrative data from hospital care were used, hence, the study included patients who required specialist care and probably suffered from a higher number of morbidities (Akazawa et al., 2019).

In latest UK study on incidence of analgesic use in patients with OA (Yu et al., 2017), joint specific prescribing patterns were not studied, and paracetamol was not included due to the risk of underestimation as a result of its availability via OTC purchase.

Patients with OA are poorly characterized with regards to their patterns of medication use (e.g. the proportion of persistent analgesic users). The information on treatment patterns, how many different medicines patients use to manage their pain is limited (Gore et al., 2011). Some studies have actually described the utilisation patterns, but these have focused on patients initiating opioids (Wright et al., 2014), carried out in specific regions within European countries (Wilson et al., 2014) or based on self-reported use of pharmacotherapies (Kingsbury, 2013). Data on how patients with OA use their medications in UK have not been comprehensively described.

2.6 Summary of Literature Review and Unresolved Issues

Despite the high prevalence of KOA in the UK, and the widespread use of different analgesics among them (Wilson et al., 2014), data on the prevalence of analgesic use in patients with KOA are limited and population level studies quantifying drug exposure, patterns of use and trends over time are lacking (Vos et al., 2012) (Wang et al., 2015) (McAlindon et al., 2014) (NICE, 2014b) (NICE, 2013b). Moreover, patients with KOA are at risk of adverse events associated with drug use (due to aging and joint pathology), however, pharmacoepidemiologic studies quantifying the risks associated with exposure to single or multiple drug classes are sparse. Falls are a

global public health challenge, and various studies have explored the association between drug use and the risk of fall but reported inconsistent findings. However, studies on the association between analgesic use and the risk of fall in patients with KOA are scarce. Importantly, it is not known if the risk of fall varies between periods of drug use and when drugs are not being used. Given the marked increase in the overall use of opioids and gabapentinoids in the UK among patients with CNCP, it is pertinent to extract condition specific data to inform practice on rationale use and optimal safety.

This research project aimed to answer the following research questions:

1. What are the temporal trends of analgesic and NP medication (antidepressants and AEDs) prescribing in patients with KOA?
2. What are the patterns of analgesics and NP medications use at an individual patient level in primary care patients with KOA?
3. What is the level of concordance in fall events recording between primary care and hospital records?
4. What is the association between any analgesic use/concomitant analgesics use and the risk of fall?
5. What is the association between current analgesic use and the risk of fall among patients with KOA?

2.7 Research Aim and Objectives

This PhD research aims to describe drug utilisation and examine the association between drug use and the risk of falls in patients with a clinician

recorded KOA in the UK. The drug classes included in the studies of this research were antidepressants and anti-epileptic drugs, opioids, NSAIDs and paracetamol.

The overarching aim of this thesis was to study prescribing trends and patterns of drug use in the population of KOA and optimise safety of drug use (in relation to fall) within this population.

The specific research objectives were

1. To select an appropriate cohort of patients with KOA from CPRD
2. To describe the prescribing trends of the following drug classes: antidepressants, AEDs, opioids, NSAIDs and paracetamol, in primary care patients with a diagnosis of KOA over the period from 2000 to 2015 stratified by drug class and year of prescribing.
3. To quantify the cumulative doses of respective drug classes utilised by individual patients and determine the proportion of persistent users within the first year of prescribing
4. To compare the recording of fall events within the first year after KOA diagnosis between CPRD and HES databases.
5. To examine the association between drug use and the risk of fall using two methodological approaches; a crude analysis and a time varying one.

2.8 Data Sources

In this research, data were obtained from the clinical practice datalink (CPRD) and the hospital episode statistics (HES) databases. A brief background on each data file included and their strengths and limitations are presented in the subsequent sections.

2.8.1 Background on the Clinical Practice Datalink (CPRD GOLD)

The Clinical Practice Datalink (formerly known as the General Practice Research Dataset) is an anonymised longitudinal ongoing primary care database, which is managed by the Department of Health, and jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare Product Regulatory Agency (MHRA) (Herrett et al. 2015).

It is the largest primary care database in the world and contains records of 17 million patients from 827 practices across the UK since its start in 1987. Currently, 337 practices contribute data to CPRD GOLD (representing 4.3% of UK general practices) with records of more than 2 million active patients (who are alive, currently registered and contribute data) being included (as of July 2019). Data are collected as part of the normal clinical care when patients consult their GPs, in participating practices. CPRD GOLD data are derived from practices using the Vision system, which is one of the standard systems used by general practitioners and is supplied by In Practice Systems Ltd (INPS). General practices contributing data to the CPRD are required to record each episode of illness, or new occurrence of a symptom,

all significant morbidity events such as diagnoses, abnormal test results and referrals and hospital admissions.

2.8.2 CPRD Data Files

Within the CPRD, data are organised in 10 separate files which include: patient, practice, staff, consultation, clinical, referral, test, therapy, immunisation and additional file (Table 1). Each data file contains a unique patient identifier (except the practice file which has a unique practice identification number) which is composed of an encrypted patient identification number and an encrypted practice identification number. The unique patient identifier allowed all records of the patient (from the 10 different data files) to be linked together (CPRD, 2019).

2.8.3 Quality of CPRD Data

All data received by the CPRD go through internal checks to ensure completeness, continuity and validation. These checks include both practice-level and patient-level quality assessments. The practice-level quality assessment is expressed as an up-to-standard status and an up to standard date from which the practice data can be used for research.

Patients are considered “acceptable” for inclusion in the CPRD if recorded details are internally consistent in the following fields: age, sex, registration details and event recording.

Regular checks that are performed by the CPRD include weekly numbers of consultations and prescriptions, completeness of prescribing, demographic, registration details, referrals and cause of death. Any data not meeting the minimum standards are removed from the database (Herrett et al., 2015). All practices are required to document 95% of prescribing and patient related events.

2.8.4 Definition of Certain Variables

I. Current registration date (crd): this is the data on which the current period of patient's registration at the practice began. This date equals the first registration date in patients who were not transferred out of the practice and equals the date of first permanent record after the last transferred out period
II. Transfer out date (tod): the date on which patient was transferred out of the practice. The field remains empty for those who were not transferred out
III. First registration date (frd): the date of first encounter at the practice or date of first permanent records.

2.8.5 Read Codes

Read coding system is a hierarchical clinical coding system of over 80,000 terms that are used to record clinical data in general practice in the UK. These codes provide standard terminology for describing the care and treatment of patients. During a patient's consultation, the GP types a

descriptive term for the symptom or diagnosis and selects the most appropriate option from a list of possible Read codes. Read terms describe signs, symptoms, diagnosis, investigations as well as treatments and are uploaded by the CPRD and added to the database for research use after necessary quality checks.

Read codes are based on the International Classification of Diseases and are widely used for many developments in the UK for example in the Quality and Outcomes framework (QOF); pay for performance scheme aimed at improving chronic disease management (NHSdigital, 2019).

2.8.6 Introduction to Hospital Episode Statistics

The HES is a database that contains information on all admissions to NHS trusts in England, including acute hospitals, primary care trusts and mental health acute hospitals. It contains details of every hospital stay, outpatient appointments and Accident and Emergency (A&E) attendances (NHSdigital, 2019).

HES data include private patients treated at NHS hospitals, or patients who were resident outside of England and care delivered at treatment centres funded by the NHS. Data are collected during a patient's stay at hospital and submitted to allow hospitals to be paid for the delivered care. HES data are also designed to enable secondary use such as use for research. The HES database is managed by NHS digital (previously the Health and Social Care Information Centre). Access to HES data is provided by CPRD

following approval of a research protocol in accordance with data governance procedures and research ethics (Herbert et al., 2017).

2.8.7 HES Data Files

HES contains over 200 million records and data are arranged into files relating to hospitalisation, episodes and events. Hospitalisation refers to the total period of inpatient hospital stay from admission to discharge. Each hospitalisation can consist of one or more episode. An episode is a time-period within a hospitalisation, which corresponds to the period where the patient is in the continuous care of one consultant using the beds of one health care provider. Data have been collected for admitted patients from 1989 onwards and each year more than 17 million consultant episodes are added to HES. In the financial year 2014/15 (April to March), 18, 731, 987 hospital episodes from 451 different NHS hospital trusts were recorded in HES admitted patient care (APC) data (NHSdigital, 2015).

For this study, the provided HES data files comprised the following: a source data file, a patient data file, a hospitalisation data file, an episode data file, diagnoses data files, a procedure data file, an augmented care data file, a maternity data file and a critical care file. The data files used in this study are described subsequently (CPRD, 2019).

2.8.8 Strengths of CPRD and HES for Health Research

2.8.8.1 Size

CPRD provides comprehensive medical records derived from the UK primary care population cross-regionally, hence data obtained are representative and generalizable to the general primary care population. CPRD also contains longitudinal data, making it ideal for the study of trends, patterns and outcomes of drug use, thus meeting the research requirements of this thesis. The large number of practices contributing data to CPRD enabled researchers to study diseases and drug use in specific regions as well as nationwide (CPRD, 2019)

2.8.8.2 Representativeness

CPRD was shown to be representative of the UK population in terms of age, sex, socioeconomic and regional distributions and current patients represent 4.3% of the UK population according to the latest UK population estimates from ONS (n=66,040,200) and as per July 2019 CPRD GOLD release.

The proportion of older adults (65 years and older) is over-represented in the HES APC database compared to the general population of England (Herbert et al., 2017). This is because HES APC covers all hospital admissions. Research showed that the CPRD-HES linked practices are also representative of the UK population in terms of age, sex and regional distributions (Padmanabhan et al., 2019).

2.8.8.3 Validity

Over the years several CPRD validation studies for a wide range of diagnoses have been conducted results of which have confirmed the validity and high quality of data.

The validation and validity of diagnosis in CPRD was investigated through performing a systematic literature review that included 357 validations investigating 183 different diagnoses including musculoskeletal disorders. The median proportion of cases with a confirmed diagnosis was 89% (range from 24-100%) and 85% utilised data from outside the CPRD to validate diagnoses (Herrett et al., 2010). HES data were validated and the median primary diagnoses accuracy was reported as 96.0% (IQR 89.3-96.3), p=0.020 (Burns et al., 2011).

2.8.8.4 Data Linkage

One of the important features of CPRD is its linkage with external data sources such as HES data, the largest hospital admissions database worldwide. The large size of both CPRD and HES provide more power than smaller studies and allow precise estimation of incidence and prevalence of conditions and/or outcomes such as occurrence of falls in primary care older adults or in a group of patients with a specific medical condition for example osteoarthritis.

Linked data were available for 390 English practices have consented for data linkage scheme (58% from total CPRD practices n= 669). Linkage between CPRD and HES is performed under appropriate governance

conditions on patients from consenting practices via a trusted third-party organisation (NHS Digital) using NHS number, post code, full date of birth and gender. In this study, the latest release of HES data linked to CPRD data was set-16 was used covering the period from 1st April 1997 to 31st August 2017. Both databases use the same unique patient identifier so records can be linked between them.

2.8.9 General Limitations of CPRD and HES

The completeness of information within the database depends on what is being entered by GPs which in turn reflects what they think is important and not necessarily what is needed for research purposes. This may have affected the incidence of both KOA as well as falls (further explained in chapters 3 and 9). Additionally, certain variables in the therapy file may be incomplete, the numeric daily doses (NDD) in particular (further explained in chapter 5). The Socio-economic status information (IMD/Townsend scores) is not recorded at all and must be obtained from a third party (NHS digital), as it is available only for HES linked practices.

HES linkage is only available for English practices (65% of total UK practices), hence studies based on linkage data have a reduced sample size and reduced power compared to studies using CPRD data.

Additionally, HES data do not include prescribing details, therefore, drug use data during periods of hospitalisation are not available which may underestimate the exposure in studies aiming at quantifying drug utilisation. Primary diagnosis in HES records is assigned by trained coders after

reading the discharge notes and is not chosen by a medical professional. This may result in potential for misclassification bias.

2.8.10 CPRD and HES for this Thesis

The CPRD was selected as a data source for its ability of provision of enough detail required for the study such as the detail of all prescriptions. Information on formulation and strength were also available. Using CPRD enabled prescription information retrieval for individual patients, which then allowed accurate quantification of both drug exposure and clinical outcomes.

2.8.11 Study and Database Period

Although CPRD data recording started in 1987, the study start date was selected to be 1st January 2000, to avoid any suboptimal recording encountered during initial periods. The end of study date was selected as it was the most up to date available data at the time of the PhD.

2.9 Ethical Approval

Access to patient data recorded in CPRD needs to be granted by the approval Independent Scientific Advisory Committee (ISAC) of CPRD. This research has secured the ISAC approval by (protocol number 18_170R) and the ISAC protocol form is included in Appendix 1 (under 1.1).

2.10 Data Management

CPRD data files were downloaded from the CPRD Gold interface and saved on the secure drive server at the University of Nottingham. Data files were in a zipped text format and included therapy, clinical, referral, consultation, additional, patient and practice files. HES data files were provided by the CPRD staff in a text format and were downloaded into the same server. All data files were downloaded, saved and subsequently unzipped by the researcher. Saved files were then imported into Stata 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) for analyses.

Data cleaning was performed prior to any analyses and involved data inspection for missing information or outliers. Patient records with missing information on year of birth (yob) were excluded as it was not possible to calculate patient's age.

Incomplete prescription data for numeric daily doses (NDD) were imputed in a stepwise approach, while prescriptions with missing prescribed quantity (QTY) were excluded. Outliers included non-plausible values of NDD or QTY (i.e. values ≥ 10 times the maximum NDD) and were treated as missing data. Details of data management (imputation of missing data) are described in chapter 5.

Chapter 3 Selection of the Overall Study Population and Incidence of Knee Osteoarthritis in Primary Care

3.1 Introduction

This chapter aims to describe the selection of the overall study population of patients with KOA from CPRD. It starts with an introduction to the definition of OA and KOA cases in epidemiologic studies using electronic health records (EHRs), followed by the methods and results on the number of selected patients. Subsequently, the annual incidence of KOA is estimated based on the selected numbers.

3.1.1 Definition of OA and KOA in Observational Studies Using Electronic Healthcare Records

Electronic healthcare records are frequently used for epidemiologic studies of OA generally and KOA specifically. Such studies are conducted for several purposes, including the estimation of incidence and risk factors for KOA (Prieto-Alhambra et al., 2014), the study of the association between socioeconomic status and the risk of KOA (Reyes et al., 2015), the study of population trends in the incidence of OA (including KOA) and initial pharmacological management (Yu et al., 2017) and the study of drug utilisation in patients with OA (Wilson et al., 2015) or KOA (Thorlund et al., 2019). Cases of OA and KOA were defined through the application of International Classification of Diseases (ICD) codes in studies conducted in the USA (Wright et al., 2014), and Europe (Reyes et al., 2015, Wilson et al.,

2015, Prieto-Alhambra et al., 2014), or by application of Read codes in UK studies using primary care data (Yu et al., 2017).

The Read code system allows clinicians to label a presenting complaint using symptom-based or diagnosis-based Read codes. Accordingly, OA may be recorded in EHRs as peripheral OA-relevant joint symptoms, i.e. peripheral joint pain, arthralgia of the joint (e.g. knee pain, arthralgia of the knee) or as a disease diagnosis, i.e. joint-specific OA diagnoses (e.g. knee osteoarthritis) (Jordan et al., 2016). There are no pharmacological treatments specific to OA, hence identification of patients in EHR records relies on the diagnostic or symptom coding (Yu et al., 2018).

Additionally, there is no single way to define OA or KOA in EHRs, and epidemiologic studies have either adopted symptom-based definitions (also known as clinical OA definition) or diagnosed OA definitions. However, the estimated prevalence and incidence rates of OA or KOA are strongly influenced by the applied definition as summarised in Table (3-1).

Table 3-1 Variation in incidence Estimates with the Applied Case Definitions

Type of KOA Case Definition	**Description of Case Definition**	**Resulting Estimates**	**Application/ Usefulness**
Clinical Case Definition	Peripheral joint symptom codes in the records	Potential overestimation of the true incidence	To estimate the burden of the condition & for service planning
Diagnosed Case Definition	KOA diagnostic codes in the records	Potential underestimation of the true incidence	When high specificity is required, no false positive cases to be included

Clinical definitions (symptom-based) prove to be more sensitive but result in considerably higher estimates compared to the more specific disease diagnosis-based definitions of OA (Yu et al., 2017, Jordan et al., 2016). For example, a study in the UK used CPRD data to estimate the incidence of KOA using diagnosis-based and symptom-based case definitions. The incidence rates were reported as 47.7 per 1000 person-years (95% CI 47.4, 47.9) with the clinical OA definition, compared to 7.9 (95% CI 7.8, 8.0) with diagnosed OA in 2013 (Yu et al., 2017).

With the application of OA relevant codes in EHRs, cases were defined with restrictive or less-restrictive algorithms based on the number of codes (single or >1) and type (outpatient or hospitalisation records). A systematic review assessed the diagnostic accuracy of OA diagnoses in administrative databases. Thirteen algorithms were assessed and classified into restrictive or less-restrictive algorithms (Shrestha et al., 2016). The restrictive algorithms required the existence of at least two codes of OA in a given time span (e.g. at least two OA diagnosis codes within two years), or a single hospitalisation record for OA (Shrestha et al., 2016). Less- restrictive algorithms required a single OA diagnostic code from an outpatient visit (Williamson et al., 2014). The authors concluded that the restrictive algorithms had lower sensitivity and high specificity and are best used to recruit patients for research like treatment trials, while the less-restrictive algorithms provided a balance between sensitivity and specificity and were more useful in studies aiming to identify all positive cases of OA (Shrestha et al., 2016). The reported sensitivities with the application of less-restrictive

algorithms in two separate studies (Coleman et al., 2015, Williamson et al., 2014) were 0.63 (95% CI 0.57-0.68) and 0.78 (0.75-0.81) and specificities 0.94 (0.88-0.97) and 0.95 (0.94-0.98) when the reference standard was medical records review.

In epidemiologic studies focussing on drug utilisation in patients with OA or KOA using EHR data, cases were defined by researchers across health systems, mostly using OA- or KOA-specific diagnostic codes rather than symptom-based codes (Table 3-2). However, a number of studies have applied both (symptom-based and diagnosis-based definitions) to provide separate prevalence and incidence estimates (Table 3-2). Predominantly, these studies applied less-restrictive definitions requiring a single record of OA or KOA code, in contrast to the restrictive definition of >1 OA code.

Guided by the definitions applied in previous drug utilisation research in patients with OA or KOA using EHRs, the present study sought to select an appropriate cohort of patients with KOA. These constituted the overall study population and drug utilisation analyses were performed subsequently on these patients.

Table 3-2 Examples of Case Definitions Applied in Drug Utilisation Studies

Author, Year	Study Aim	OA/KOA Case Definition Codes	Records
Gore, 2011	To examine comorbidities, pain- related pharmacotherapy and direct medical costs of patients with OA (including KOA)	Diagnosis of OA using ICD-9-CM codes (715.XX) corresponding to osteoarthritis and allied disorders	Single record
Wilson, 2014	To examine the prevalence of drug use in patients with OA (including KOA) in Spain.	ICD diagnostic codes of OA including M17 corresponding to osteoarthritis of the knee	Single record
Wright, 2014	To investigate the use of opioids in older adults aged ≥ 65 years with KOA in 2003, 2006 and 2009 in the USA	KOA cases were defined as those with ICD-9 diagnostic codes for OA of the knee (715.x6) OR knee pain (719.46) plus unspecific OA codes 715.x8, 715.x9 or 715.x0	Single record OR >1 record
Yu, 2017	To determine trends in the rate and pharmacological management of new cases of OA (including KOA) in the UK.	Two separate case definitions: **Clinical OA**: using joint pain codes including knee pain codes. **Diagnosed OA:** including diagnostic codes for KOA	Single record
Thorlund, 2019	To quantify opioid use in patients with KOA and hip OA in Sweden	ICD-10- diagnostic codes: M17 corresponding to osteoarthritis of the knee	Single record

3.2 Study Aim and Objectives

The aim of this study was to describe the process of selection of an appropriate cohort of patients with KOA on which further analyses of drug utilisation could be carried out. Additionally, to validate the cohort selection method and resulting numbers, the study aimed to estimate the annual incidence of KOA diagnosis among primary care patients using CPRD data.

Specific objectives were:

1. To select patients with KOA using both KOA diagnosis and symptom-based Read codes in the CPRD
2. To compare the numbers of selected patients resulting from the application of each cohort selection strategy to justify the chosen final strategy
3. To determine the number of patients with KOA that constitutes the overall study cohort for the present research
4. To determine the annual number of patients with an incident diagnosis of KOA recorded between 2000 and 2015, and to compare the incidence of KOA with estimates reported in Europe and the UK.

3.3 Methods

3.3.1 Study Design

This observational study applied a cross-sectional design between 2000 and 2015.

3.3.2 Knee OA Code List Development

The development process for the Knee OA code list started with the generation of a list of osteoarthritis-diagnosis-related codes using different Read terms, including: *arthritis* *osteoarthritis* and *arthrosis* through a search of the medical browser dictionary of CPRD. Additionally, a separate search for Read codes starting with N05* (osteoarthritis and allied disorders) was also performed using the browse function of CPRD. The results of both

searches were combined to generate a single list containing all OA relevant codes, while the codes for other arthritis conditions (e.g. rheumatoid arthritis) were saved separately.

Alongside, a list of Read codes for OA (including KOA) was compiled from a free clinical codes repository established by the University of Manchester (www.clinicalcodes.org) and from the supplementary code files of relevant publications (Kontopantelis et al., 2015). A list of OA Read codes was then generated by merging the codes derived from both sources and removing any duplicates. Knee joint pain codes were compiled using a similar method (Appendix 1, Table 1.2).

3.3.3 KOA Definitions Applied in the Present Research

Informed by the KOA definitions applied in previous drug utilisation studies as presented in Table 3-2, including definitions based on KOA diagnostic codes, or symptoms codes or both, the present study applied five different cohort selection strategies to inform the justification of the final cohort selection. These strategies differed in their sensitivity to define cases of KOA and to select cohorts of patients with KOA. The strategies were the result of the application of KOA diagnostic codes, symptoms codes or both, as detailed below and summarised in Figure 3-1 and Table 3-3.

a) Cohort Selection Strategy 1:

This strategy required the existence of a single record of a clinician-recorded diagnosis of KOA within patients' data to satisfy the definition of KOA cases. The rationale was based on the consideration of the overall aim of this

research being to study the utilisation of drugs among patients with true KOA, and not any other knee joint pathologies. Read codes compiled for this strategy included nine codes that described diagnosed possible and definite KOA cases (Table 3-3).

b) Cohort Selection Strategy 2:

This strategy was also based on KOA diagnostic codes, however it only included Read codes that corresponded to definite KOA cases (but not any possible cases). The compiled codes included three codes that described KOA diagnosis clearly and precisely (Table 3-3).

c) Cohort Selection Strategy 3:

This strategy applied Read codes that were published by Arden et al. (Nigel Arden, 2017). In their work to develop a tool to predict the outcomes and failures of lower limb arthroplasty using CPRD data, the medical diagnosis of KOA was based on two definite medcodes (corresponding to the Read terms: knee OA and OA of Knee, NOS) (Table 3-3).

d) Cohort Selection Strategy 4:

This strategy required the existence of codes related to any knee pain (i.e. clinical KOA definition) (Appendix 1 Table 1.2) or any KOA diagnostic codes in the patients' records. This strategy allowed cohort selection based on either symptoms or diagnostic Read codes in their records. It may, however, have included patients with acute knee pain conditions and not necessarily KOA cases.

e) Cohort Selection Strategy 5:

This required at least one code of knee pain in addition to any KOA diagnosis medcode to define KOA cases. It implied a restrictive case definition requiring two KOA-related codes and it represented a group of patients who were diagnosed with KOA and also experienced pain symptoms. The above strategies are presented in Figure 3-1 &Table 3-3.

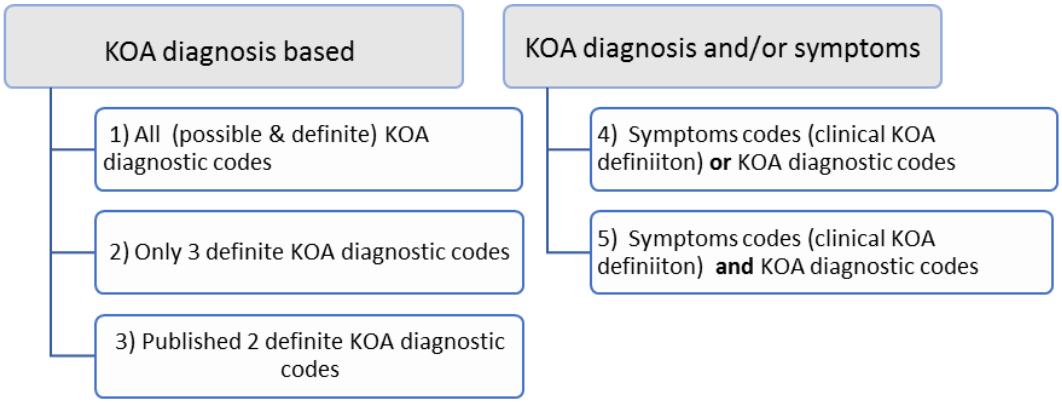


Figure 3-1 Summary of the Five Cohort Selection Strategies

Table 3-3 Cohort Selection Strategies Applied for Final Cohort Selection

Strategy	Code Type	Description	Read Terms Used	No. Records*
1	KOA diagnostic	Nine codes (definite and possible KOA cases)	- Localised OA of the lower leg (3 codes) - Arthrosis (2 codes) - Knee OA - OA of Knee, NOS - Patellofemoral OA - Tibiofibular OA	Single
2	KOA diagnostic	Three KOA specific codes (definite codes only)	- Knee OA - OA of Knee, NOS - Patellofemoral OA	Single
3	KOA diagnostic	Two KOA specific codes (definite codes only) obtained from published work	- Knee OA - OA of Knee, NOS	Single
4	KOA Symptoms **or** KOA diagnostic	This definition ensured maximum sensitivity	Symptom-based Read terms were: knee pain, arthralgia of the knee, knee joint pain **or** Read terms from strategy 1	Single
5	KOA Symptoms **and** KOA diagnostic	This definition ensured maximum specificity	Read terms from strategy 1 **and** 4	>1 record

NOS: not otherwise specified *number of records of relevant KOA codes required for a case definition

The set of Read/medcodes corresponding to each strategy were then applied in the define tool of the CPRD. Subsequently, the number of patients resulting from each strategy was documented and compared to inform the final cohort selection strategy.

3.3.4 Inclusion Criteria

Patients were eligible for inclusion in this study if:

1. They had a recorded diagnostic for symptoms based Read Code of KOA in their clinical referral records of CPRD.

2. The diagnosis/symptoms' Read code was recorded at the age of 18 years or over.
3. The diagnosis/symptom was recorded between 1st January 2000 and 31st December 2015.
4. The diagnosis/symptom occurred at least 12 months after registration and was recorded on or after the practices' up to standard (uts) date.
5. The diagnosis/symptom of KOA must also have been recorded before the earliest of; end of the study date (31st December 2015), transfer out date or death date.

3.3.5 Exclusion Criteria

Patients who were less than 18 years at KOA diagnosis/symptom and those who were registered for less than a year prior to study initiation were not included. Patients with a diagnosis of inflammatory arthritis, such as rheumatoid arthritis and systemic lupus erythromatousus (SLE), identified by appropriate Read codes, were excluded. Inflammatory arthritis has a distinct pathophysiology where inflammation plays a major role and its management involves prescribing disease-modifying anti- rheumatoid drugs (DMARD) as a main treatment modality. Such drugs were not the focus of the present thesis.

Patients with KOA who had a recorded cancer diagnosis at any time during follow-up were identified and excluded after the estimation of KOA incidence (as detailed in section 3.4.6). Rheumatoid arthritis, Systemic Lupus Erythematosus (SLE) and cancer diagnoses codes were obtained from the

University of (Cambrige, 2018) and from the Quality and Outcome Framework (NHS, 2017b) (see Appendix1, Table 1.3).

3.3.6 Study Outcomes

This study measured the following outcomes:

1. The total number of patients with KOA during the study period.
2. The annual incidence of KOA between the years 2000 and 2015. This was calculated with an estimated at-risk population from the CPRD population during the respective year.
3. The length of follow-up in years and the proportion of patients with relatively long and short follow-up periods.

3.3.7 Data Extraction

The finalised KOA-related Read codes were then applied in the ‘Define’ tool of CPRD GOLD, and subsequently a cohort of eligible patients was identified, i.e. a list of patients resulted from the define function.

The list of patients generated in the define tool was then used in the ‘Extract’ tool to retrieve all the data associated with these patients, including multiple text files extracted from clinical, consultation, immunisation, patient, practice, referral, staff, test, therapy and additional files in the CPRD. Except immunisation files, all the aforementioned records were extracted from the September 2016 build of data.

3.4 Results

3.4.1 Number of Selected Cases Through Cohort Selection Strategies

The numbers of selected cohorts varied with the applied strategies, as presented in Table 3-4 and illustrated in Figures 3-2 to 3-4.

Table 3-4 Number of cases with the application of cohort selection strategies

Strategy	**Description**	**Resulting Numbers of Selected Cases**
Diagnosis-Based Strategies		
strategy 1	All KOA diagnostic codes (definite and possible)	139,333
strategy 2	Three definite codes	137,541
strategy 3	Published codes of KOA (two definite codes)	134,499
Diagnosis and/or Symptoms-Based Strategies		
strategy 4	KOA-knee-pain-related codes or KOA diagnostic codes	898,690
strategy 5	Restrictive case definition strategy	83,294

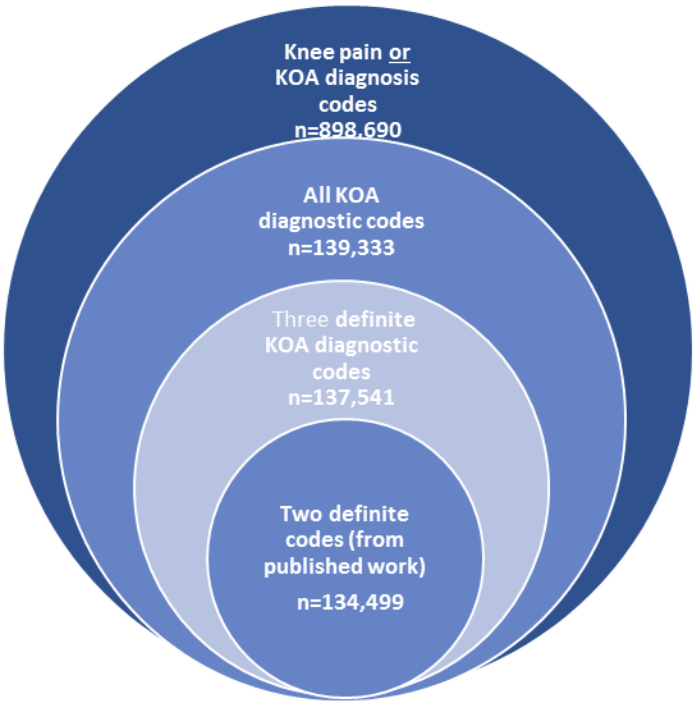


Figure 3-2 Number of Patients Selected by the Application of Strategies Based on Diagnostic Codes **or** Symptoms Codes

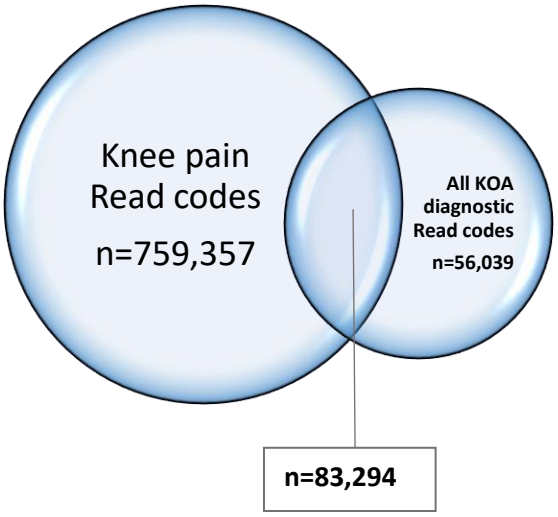


Figure 3-3 Number of Patients with KOA Selected with the Application of Diagnostic and Symptoms Codes

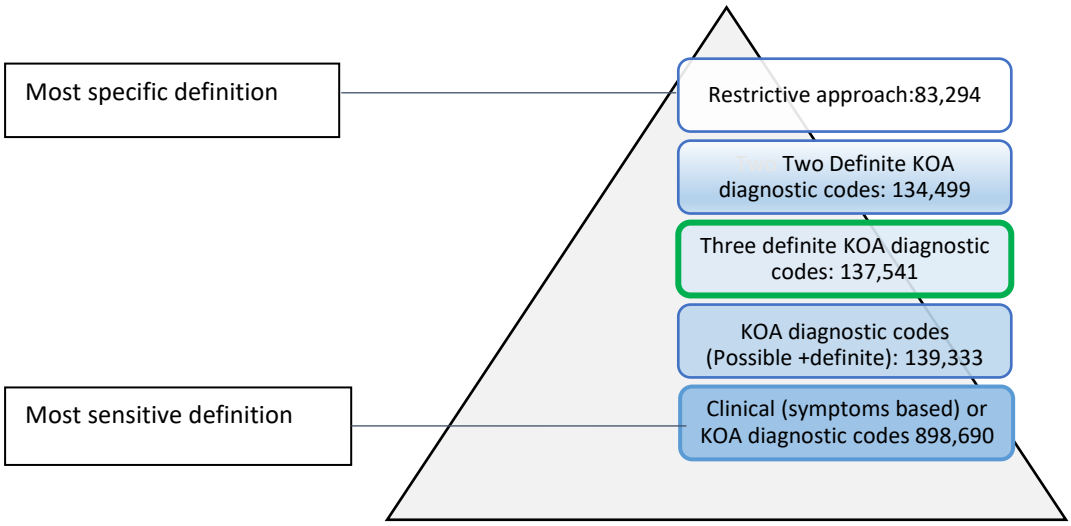


Figure 3-4 A Schematic Illustration of the Selected Patients in Order of Numbers Identified per Strategy

Figures 3-2, 3-3 and 3-4 illustrate the difference in the number of patients obtained by the application of various cohort selection strategies. The greatest number of patients was selected with the application of the most sensitive strategy (strategy 4) and the smallest number was selected with the most restrictive strategy (strategy 5). The selection of the highest or lowest estimates for the final KOA cohort may result in the over- or under-estimation of the true numbers. Hence, strategies 4 and 5 were not considered for final cohort selection. In between were the diagnosis-based strategies (Figure 3-4), which were judged to be most appropriate for the final cohort selection of this research.

3.4.2 Final Cohort Selection

Among strategies 1-3, the final cohort selection was founded on a balanced approach, i.e. the intermediate one seen in strategy 2, which revealed

137,541 patients (Figure 3-4). This avoided a potential under-estimation by excluding true KOA cases (as in strategy 3), and at the same time avoided the unnecessary inclusion of patients with a possible (not definite) diagnosis of KOA (as in strategy 1).

This strategy (strategy 2), which was based on the diagnostic codes of KOA, ensured that an optimal number of patients was selected for further analyses by avoiding the over-estimated numbers obtained by the application of knee pain related codes and the under-estimated numbers when knee pain plus KOA codes (restrictive algorithm) were applied (Figure 3-4). It also avoided the inclusion of patients with possible KOA (as in strategy 1), which could have led to a slightly over-estimated total cohort. There were 490 patients diagnosed outside the uts date and these were excluded from the selected cohort, leaving a final cohort of 137,051 patients (Figure 3-5).

In summary, the final study cohort included all CPRD patients who had at least one KOA diagnosis record (corresponding to any of the three selected Read codes) in their clinical or referral files between 1st January 2000 and 31st December 2015 (Figure 3-5). The overall approach for cohort selection was endorsed by the consultant clinician on the research team.

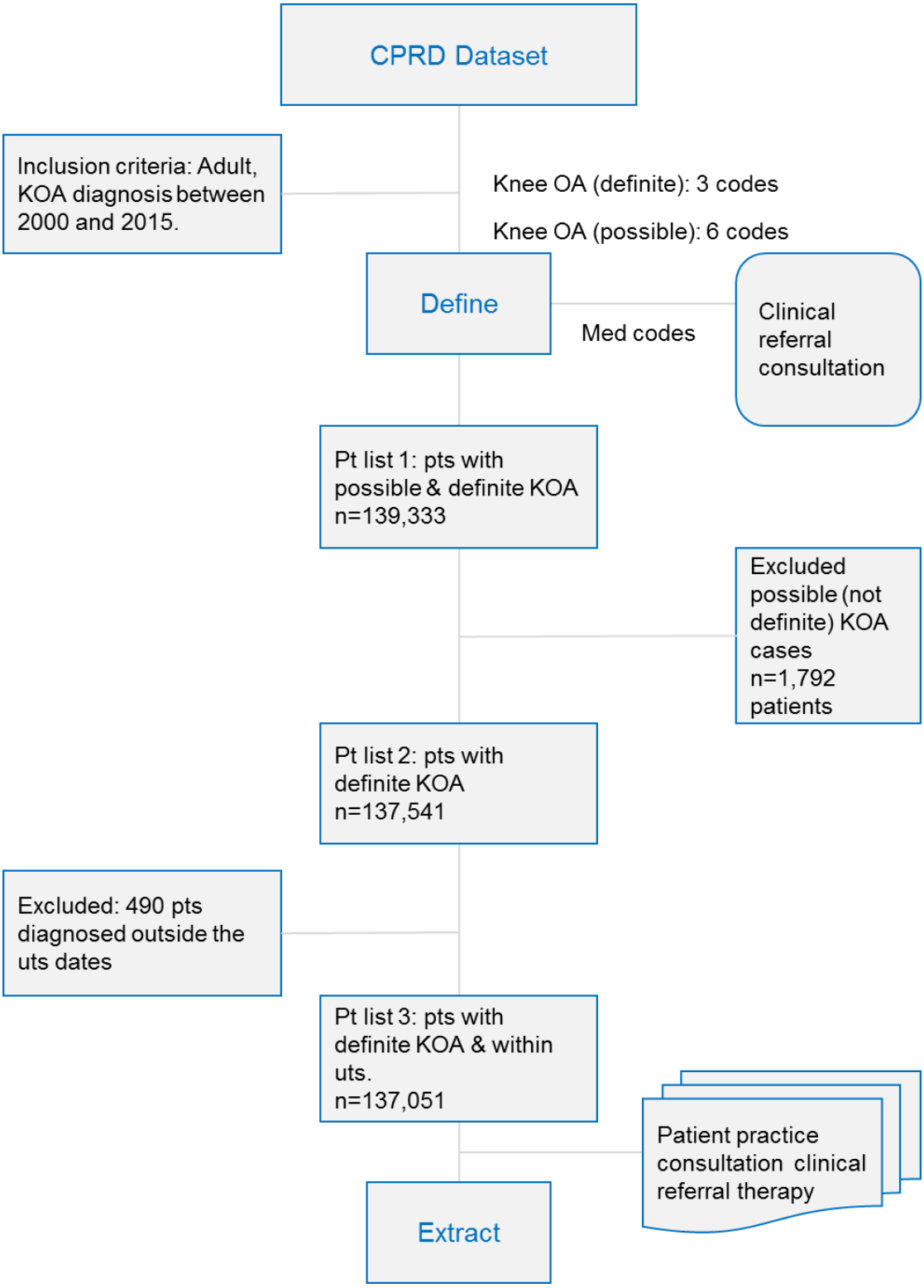


Figure 3-5 Diagram of Study Cohort Selection Based on KOA Diagnosis

3.4.3 Number of CPRD Registrants

The number of active CPRD registrants increased between the years 2000 and 2002 and remained stable thereafter until 2013, with an observed decrease in 2014 and 2015 (Figure 3-6).

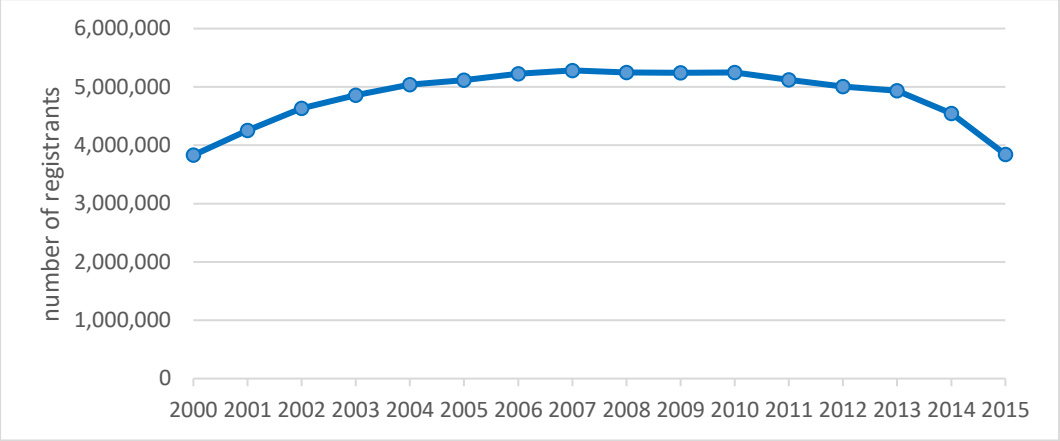


Figure 3-6 Number of Active Registrants in CPRD Over the Study Years

3.4.4 Demographic Characteristics of the Identified Patients with KOA

After application of the final cohort identification strategy, this study included 137,051 patients with KOA. In total there were 79,936 females (58.3%) and 57,115 (41.7%) males with a mean age (SD) at diagnosis of 67.4 years (12.67) and 65.2 years (12.41) respectively. Most of the identified patients were between 40 and 80 years old at the date of KOA diagnosis (n=113,603) representing 82.9% of the total cohort. The proportion of females was higher across most categories, except in those younger than 40 years (Figure3-7). A total of 125,096 out of the total identified cohort had a new diagnosis of KOA within the study period and their demographic characteristics are presented in Table 3-5.

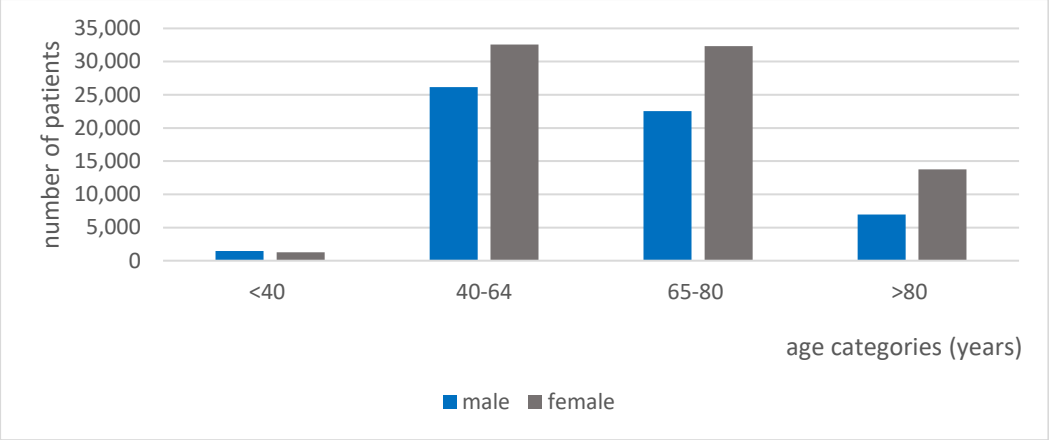


Figure 3-7 Number of Patients with KOA by Gender and Age Categories

Table 3-5 Number and Demographic Characteristics of Patients with Incident KOA

Characteristic	No. Patients with an Incident Diagnosis of KOA Between 2000 and 2015
Total	125,069
Gender	
Females (%)	72,896 (58.3)
Males (%)	52,173 (41.7)
Mean age (SD)	66.73 (11.25)
Age ranks (years)	
<40	2,279 (1.8)
40-64	52,102 (41.7)
65-80	50,496 (40.4)
>80	20,192 (16.1)

SD standard deviation

3.4.5 Annual Incidence of KOA Diagnosis

The annual number of patients with an incident diagnosis of KOA during the study years ranged between 5,098 in 2000 and 9,274 patients in 2008. The number of patients with an incident diagnosis of KOA per 1000 CPRD registrants ranged from 1.33 per 1000 CPRD registrants in 2000, 1.76 in 2008 and 1.45 patients in 2015 (Figure3-8). The incidence of KOA remained

stable through the years between 2009 and 2015 at 1.73 to 1.45 per 1000 CPRD registrants respectively.

Compared to males, the incidence of KOA diagnosis was higher in females throughout the study period (Figure 3-8). The incidence of KOA was estimated for each age rank (Figure 3-9). Patients with an incident diagnosis of KOA were predominantly aged between 65 and 80 years, followed by those aged between 40 and 64 years.

The incidence of diagnosed KOA among the 65 to 80-year-old age group was 0.68 per 1000 CPRD registrants in 2000 and it remained stable until 2015 with a recorded incidence of 0.67 per 1000 registrants. Among those aged between 40 and 65 years, the incidence estimates were 0.30 and 0.54 per 1000 CPRD registrants between the years 2000 and 2015 respectively.

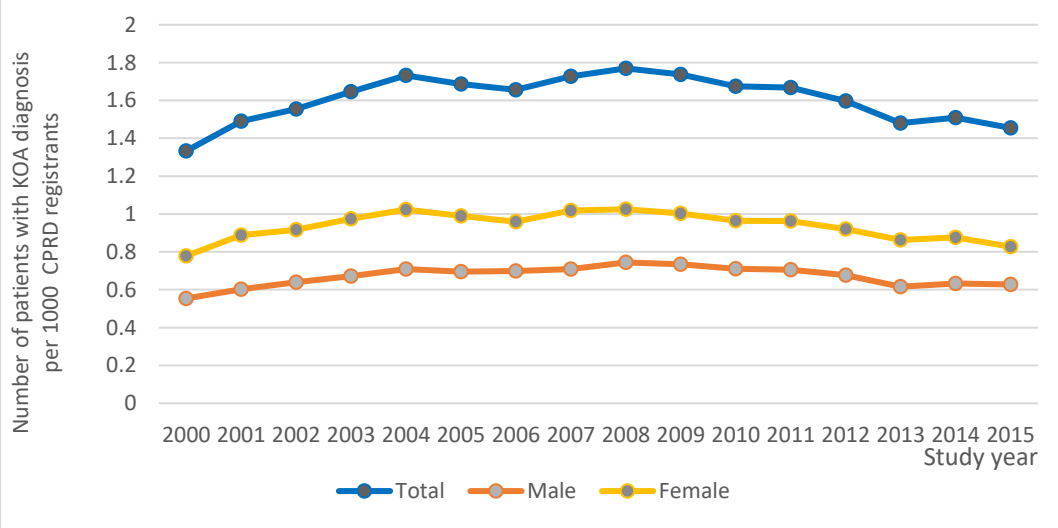


Figure 3-8 Annual Incidence of KOA Diagnosis by Gender

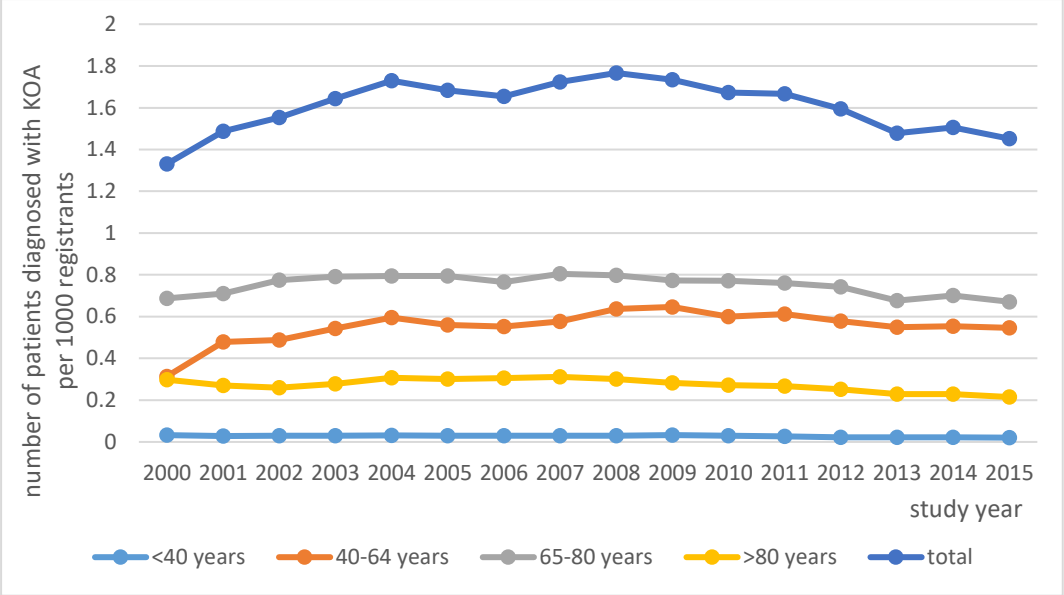


Figure 3-9 Annual Incidence of KOA Diagnosis by Age Rank

3.4.6 Selection of Patients with Cancer Diagnoses

Within the selected cohort of patients with KOA (n=137,051), those with any recorded cancer diagnoses were selected and excluded from drug utilisation analyses and the subsequent research studies of this thesis. The number of identified patients with at least one recorded cancer diagnosis was 19,414 (14.1%). The remaining final number of patients with KOA was 117,637 (after excluding patients with cancer diagnoses).

3.4.7 Length of Follow-up

Around 17.5% of the patients were followed up for 1-3 years (n=26,110) after KOA diagnosis, and 19.1% of the patients were followed up for 7 to 10 years (n=23,993) (Figure 3-10). The median follow-up since KOA diagnosis was 5.9 years (IQR 2.9, 9.6).

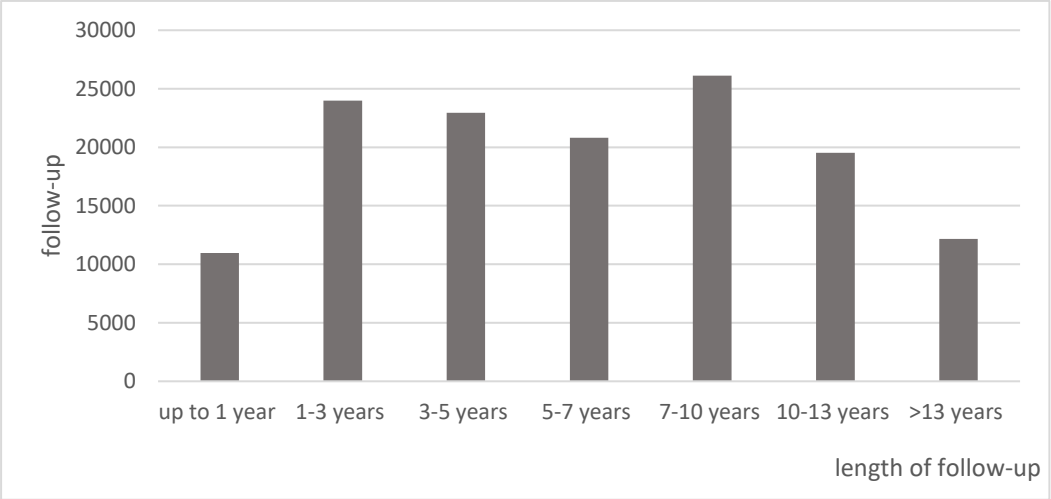


Figure 3-10 Length of Follow-up after KOA Diagnosis

3.5 Discussion

3.5.1 Main Findings

This study selected a total of 137,051 patients with a clinician-recorded diagnosis of KOA between 1st January 2000 and 31st December 2015. The cohort selection was concluded (finalised) after comparing the resultant case counts of several case- finding strategies. Case counts ranged from 898,690 (resultant of the most sensitive strategy) to 83,294 (from the most specific strategy). Subsequently, the annual incidence of KOA diagnosis was measured, stratified by gender and age groups. The overall incidence ranged between 1.3 and 1.4 per 1000 CPRD registrants in 2000 and 2015, respectively.

3.5.2 Justification of Final Cohort Selection Strategy

The final cohort selection strategy was optimised by the application of several strategies using both KOA diagnostic and symptoms codes, with less restrictive and restrictive algorithms.

Due to the potential risk of over-estimation of the true case counts, this study did not consider clinical definitions (knee pain/symptoms) for the final cohort selection and used diagnosis-based codes instead. Higher numbers of patients with a clinical definition compared to diagnosed OA was a consistent finding in the literature; with a total of 1,716,253 incident cases of clinical OA compared to 432,163 cases of diagnosed OA in a study using CPRD data (Yu et al., 2017). The estimated incidence rates were 47.7 per

1000 person-years (95% CI 47.4, 47.9) with a clinical OA definition compared to 7.9 (95%CI 7.8, 8.0) with diagnosed OA in 2013 (Yu et al., 2017). Similarly, Jordan et al. found 616 diagnosed OA patients compared to 811 with a clinical definition, out of a total of 13,831 patients in their cohort study using data from a regional EHR database (Jordan et al., 2016).

Despite the potential risk of over-estimation with the use of symptoms-based codes, a study found no significant difference in analgesic prescribing between patients with diagnosed OA and those with joint pain. This suggested that diagnosed OA does not influence the choice of analgesia in primary care (Jordan et al., 2016). However, more recent evidence suggested that analgesics (NSAIDs and opioids) were more likely to be prescribed to incident cases with diagnosed OA than to cases with clinical OA (Yu et al., 2017). For example, the proportion of patients receiving a prescription for weak and strong opioids was 14.0% and 0.5% for clinical OA and 19.7% and 1.2% for diagnosed OA cases respectively in 2013 (Yu et al., 2017).

This implies that the use of symptoms-based case definitions of KOA may potentially underestimate the prevalence of drug use in this population. Hence, the use of KOA diagnostic codes to define KOA cases was justified as it not only ensured the inclusion of definite cases of KOA, but it also avoided a potential under-estimation of drug use. Eventually, this would aid the estimation of reliable drug utilisation from the succeeding research studies within this thesis.

Among the diagnosis-based strategies (1, 2 and 3), this study excluded strategy three, which involved the application of just two definite KOA diagnosis codes, leading to a potential (slight) under-estimation. Furthermore, strategy one was excluded too, due to the potential for over-estimation as a result of the inclusion of possible (not definite) cases of KOA. The final strategy (strategy 2) provided a balance across the applied strategies as it avoided both over- and under-estimation of the true counts and was therefore a justified approach for cohort selection for further analyses within this research.

3.5.3 Comparison of Final Cohort Selection Method and Resulting Case Counts with Other Studies

In contrast to the more restrictive case-definition algorithms implemented in studies requiring multiple records of KOA codes to ascertain diagnosis (Rahman et al., 2016), the present study required a single record of KOA diagnosis within the CPRD during the study period. A single OA diagnosis code was a standard definition used in several previous epidemiological studies (van der Waal et al., 2006, Yu et al., 2015, Yu et al., 2017) as well as drug utilisation studies (Wilson et al., 2015) and evidence showed that only 1.3% of cases defined in this way are subsequently given a different diagnosis (Prieto-Alhambra et al., 2014). This provided further reassurance on the adopted final cohort selection strategy.

Similar to the case definitions used in previous drug utilisation studies in Europe and the UK, the present study applied diagnostic codes to define

cases with KOA in CPRD. For example, a study in Sweden was conducted to quantify the utilisation of opioids in patients with KOA and/or hip OA, including 751,579 residents aged 35 years or older in Skane. The study used KOA diagnostic codes, which resulted in the selection of 53,290 patients with prevalent KOA (7%) in 2015 (Thorlund et al., 2019). In Spain, Wilson et al. found a total of 96,222 patients with diagnosed KOA over a period of 5 years, which represented 2.9% from the total registered population in the SIDIAP (Sistema de Información para el Desarrollo de la Investigación en Atención Primaria) database and aged 40 years or over (n=3,266,862) (Wilson et al., 2015). In the UK, 432,163 patients with diagnosed OA were identified between 1992 and 2013 using CPRD data; however, joint specific prevalence estimates were not published (Yu et al., 2017).

The present study selected 137,541 patients, who represented 3.4% of the CPRD population (CPRD population n=4,000,000 patients). This overall prevalence over a period of 16 years was close to/comparable to that reported in the Spanish study (2.9%) (Wilson et al., 2015).

3.5.4 Comparison of Patients' Demographic Characteristics with Other Studies

The average age (SD) of the identified patients was 66.30 (12.54) years, females were older than males and constituted the majority (58.3%, n=79,936) within the identified cohort. The higher proportion of females compared to males was also consistent with previously reported findings from Spain using data from a large Catalan database where male patients

constituted 35.5% of the total number of identified patients with KOA (n=96,222) (Prieto-Alhambra et al., 2014). In the UK, using data from the CPRD in 2001, the consulting prevalence of OA was reported for females as 206 per 10,000 registrants aged 15 years or more , whereas for males it was 120 per 10,000 registrants (Jordan et al., 2007b).

3.5.5 Comparison of the Annual Incidence of KOA with Other Studies

The incidence of KOA reported in the present study was broadly similar to estimates reported in other studies from Europe and Canada.

The incidence of KOA found in the present study was similar to that reported in Dutch primary care practices using data from 96 practices in the second Dutch National Survey of General Practice (van der Waal et al., 2006). The incidence of KOA was reported to be 1.5 per 1000 persons in 2001, which was similar to the estimated incidence of 1.48 per 1000 CPRD registrants in the same year obtained from the present study.

However, the reported KOA incidence in the present study was lower than that estimated in a previous UK-based study (Yu et al., 2015). In the UK, the reported incidence of KOA was reported as 2.9 per 1000 persons in the year 2010 (Yu et al., 2015) which was higher than the estimate of 1.67 per 1000 CPRD registrants estimated in the present study for the year 2010. Such a difference can be attributed to the fact that the data in the study by Yu et al. (2015) were obtained from a local primary care database in North Staffordshire in England which includes 11 general practices within a confined region of England (total practice patient population of 94,955),

while the present study used data from a large nationally representative database. North Staffordshire is more deprived than England as a whole, and this might have led to higher estimates of KOA incidence. Socioeconomic deprivation has been associated with a higher incidence of OA and the most deprived areas had a higher risk of KOA compared to least deprived areas, with an incidence rate ratio (IRR) of 1.23 (95% CI 1.19-1.28) after adjustment for obesity (Reyes et al., 2015). Therefore, the differences in the included population may have led to the differences in incidence estimates between the published study (Yu et al., 2015) and the present study.

The present study found that the incidence of KOA varied by gender; females had a higher incidence compared to males throughout all the study years, which was consistent with previous research findings. In the UK, the primary care consultation incidence of diagnosed KOA in females was 2.1, while in males it was 1.6 per 1000-person years in 2013 (Yu et al., 2017). Similarly, the incident rate (95% CI) of diagnosed KOA in a population-based study in Spain was 8.3 (8.2, 8.4) per 1000-person years in females compared to 4.6 (4.5, 5.7) per 1000-person years for males (Prieto-Alhambra et al., 2014).

The present study reported a varied incidence of diagnosed KOA across age ranks, with patients aged between 65 and 80 years being the most prominent group. This finding was in line with findings of OA in the UK, where the incidence of OA in any joint peaked at 75 to 84 years, slightly reducing at 85 years and over (Yu et al., 2015). Similarly, the incidence

varied with age and was highest in those aged between 65 and 80 years in a Canadian study population (Rahman et al., 2016).

The final cohort of patients with KOA selected for the subsequent studies in this thesis excluded patients with any cancer diagnosis in their entire record. Patients with KOA with a cancer diagnosis may have different analgesic requirements than those without any cancer and this may therefore result in over- or under-estimation of analgesic prescribing prevalence. For example, in a cohort of primary care patients prescribed strong opioids, morphine prescriptions constituted 61.4% of all prescriptions for those with a cancer diagnosis, compared to 47.3% of total prescriptions in those with a non-cancer painful condition. In the same cohort, buprenorphine prescriptions constituted 4.7% in the cancer group compared to 18.6% in the non-cancer group (total number of included prescriptions was 2,672,022) (Zin et al., 2014). Such a variation may lead to biased results of drug utilisation prevalence and outcomes.

3.5.6 Strengths and Limitations

This study has identified a cohort of patients with a diagnosis of KOA using specific Read and medical codes. The incidence of KOA diagnosis over the study years was generally similar to the estimates reported from other countries using EHRs. The demographic characteristics and the variation of incidence of KOA diagnosis with gender and age were also in line with estimates published in the literature.

In the present study, a patient was labelled as an incident case with the maximum look-back period. The look-back period is an observation time required to eliminate prevalent KOA cases, and it affects the estimated incidence rates in EHRs (Yu et al., 2015). Each patient's records were checked for the existence of any KOA diagnosis codes, and patients were considered incident cases if no such record existed in their entire previous record. Research showed that a 10-year period was a reasonable maximum period to detect any existing diagnosis of KOA, as reported in a previous study (Kopec et al., 2008). However, this study conservatively applied the maximum look-back period available for each patient. A similar approach (maximum look-back period) was also applied in a previous UK study using the CiPCA data base; however, that period was no longer than 10 years (Yu et al., 2015).

Nonetheless, this study has some limitations, mainly related to OA recording in CPRD. The use of diagnosis-based codes may have under-estimated the incidence of KOA, resulting from clinicians using the presenting symptoms codes. However, patients consulting for knee problems are more likely to have a recorded KOA than those consulting for problems in other sites e.g. hip, foot and ankle (Jordan et al., 2016).

Knee OA is a long-standing morbid condition. Diagnosis may have been recorded but did not appear in the chosen study period. The measure of occurrence will be affected by the length of time period chosen. However, research has shown that it is likely that the diagnosis of OA will be documented in the records over a time period of 7–10 years (Jordan et al.,

2016). Furthermore, the incidence of KOA reported in the present study may potentially be underestimated as it only reflects the estimated consultation incidence (the rate of new cases presenting to primary care). Nevertheless, the primary care setting is the setting where the majority of patients with OA or KOA are diagnosed and managed.

3.6 Conclusion

The present study selected a valid cohort of patients with a clinician-recorded KOA diagnosis from CPRD data (n=137,051). The final cohort selection was informed by the case counts obtained from several case-finding strategies, which led to minimised KOA misclassification in the final cohort. To validate the identified cohort, the annual incidence was estimated between 2000 and 2015, and it was found to be in general agreement with published data.

Chapter 4 Drug utilisation in Primary Care Patients with Knee Osteoarthritis

4.1 Introduction

Drug utilisation research in patients with OA has focused on the prevalence and changing trends of analgesic prescribing over time, primarily by measuring the annual prescription prevalence and the proportion of patients using each analgesic over various periods of time, ranging from one (Gore et al., 2011) to 22 years (Yu et al., 2017). However, drug utilisation using common pharmacoepidemiologic measures (e.g. defined daily dose (DDD) and annual days of supply) was not addressed, hence population-level information remains limited. Moreover, the extent and characteristics of exposure to antidepressants and AEDs for patients with OA or KOA – is understudied, with only one recently published study on the use of gabapentinoids in patients with OA in the UK (Appleyard et al., 2019).

The detailed analysis of changes in drug prescribing prevalence over time would identify the time points of any unexpected change, which can then be linked to any regulatory, advisory or educational measures. For example, temporal changes in the prescribing prevalence of analgesics were demonstrated using prescriptions in the Primary Care Archive (CiPCA), an English regional database (Bedson et al., 2013). These changes were influenced by national advice and guidelines on analgesic safety between 2004 and 2009 (Bedson et al., 2013).

Such findings provided insights regarding major influences on prescribing and aided the overall understanding of prescribing patterns of analgesics within primary care over the given time periods. Therefore, observing the prescribing trends of a broader range of medications – including antidepressants and AEDs, in addition to the conventional analgesics, opioids, NSAIDs and paracetamol – used for OA-related pain management is a key component of data geared towards rational prescribing and optimal drug safety for the population of patients with KOA.

To address the existing limitations in research on drug utilisation in patients with OA, the present study sought to describe the temporal changes in the prescribing in primary care patients with KOA in the UK. The findings also provide the background context of the investigations in the subsequent chapters of this thesis.

4.2 Study Aim and Objectives

This study aimed to describe the changes in prescribing of the following drug classes, antidepressants, AEDs, opioids, NSAIDs and paracetamol, in primary care patients with a diagnosis of KOA over a period of 16 years (from 1st January 2000 to 31st December 2015). The specific study objectives were:

1. To quantify the utilisation of each of the study drug classes through the following repeat annual measures:
    1. Number of prescriptions
    2. Number of defined daily doses (DDD) per day

3. Oral Morphine Equivalent (OMEQ) dose per day
4. Number of days of drug supply

2. To estimate the annual prevalence and incidence of drug use amongst patients with KOA (i.e. number of existing and new users of each drug class among patients with KOA)

4.3 Methods

4.3.1 Study Design

This observational study employed a cross-sectional design over the period of January 2000 to December 2015 to study the prevalence and trends of drug prescribing for primary care patients with KOA, using data from CPRD.

4.3.2 Study Subjects

To study the drug prescribing trends, all patients with a recorded diagnosis of KOA made between January 1st, 2000 and December 31st 2015, and aged 18 years or over, were included. Observation of the cohort members began from the date of the first prescription of the drug after the latest of the following dates: 1st Jan 2000, up-to-standard (uts) date, or registration date. Observation continued until the earliest of the following dates: 31st Dec 2015, date of transfer out, last collection date in CPRD, or death date. Prescribing records for antidepressants, AEDs, opioids, NSAIDs and paracetamol were extracted from CPRD therapy files using specific drug-related product codes.

The CPRD provides an inbuilt product dictionary in which medical products of interest can be searched, and the corresponding product codes identified. The identification of product codes is achieved by specifying either the drug substance name or the British National Formulary (BNF) code of the chapter and section of the drug in the dictionary. Drug names for each of the study drugs were identified in the CPRD inbuilt product dictionary. This generated a list of product codes which included both the generic and brand names for each of the drug classes.

The product code lookup file was searched also for the product codes of the study drugs. The search was mainly based on the respective BNF sections: antidepressants were those described in BNF section 4.3, AEDs were those described in section 4.8.1, opioids in section 4.7.2, NSAIDs in section 10.1.1, and paracetamol in section 4.7.1 of the BNF. Duplicate codes were removed, and a master list of each drug's product code was generated.

Within opioids, buprenorphine 2mg and 8mg tablets were excluded, as these are almost exclusively prescribed for the treatment of opioid dependence. Injections and suppositories were excluded too, as these formulations are less likely to be prescribed in primary care for the long-term management of KOA-related pain.

The list of product codes generated was then applied to all extracted therapy files. This identified prescription records containing antidepressants, AEDs, opioids, NSAIDs and paracetamol within the therapy files. Each prescription was required to be within the up-to-standard date (the date at which the practice was deemed to be of good quality for research based on CPRD

internal quality control standards) and patients' practice registration dates. Extracted prescriptions were then saved for further descriptive analysis. Study drugs and corresponding product codes are presented in Appendix 2.

4.3.3 Study Measures

This cross-sectional study measured prescription data for adults with a diagnosis of KOA who were identified during the study period. The following study outcome measures were calculated separately for each drug class in each calendar year.

4.3.3.1 Number of Prescriptions

The total number of prescriptions for each study drug class was measured on an annual basis from January 2000 to December 2015, and the number of prescriptions per 1000 CPRD registrants per year was calculated.

4.3.3.2 Prevalence of Study Drug Users

The annual prevalence of each of the study drug class users from 2000 to 2015 was measured by dividing the total number of patients who were prescribed at least one prescription of the study drugs during the year of study (numerator) by the total number of adult patients in the same year (denominator). The result was then multiplied by 1000 to generate the number of patients prescribed the particular drug class per 1000 CPRD registrants. Patients who were prescribed any of the study drugs in more

than one of the study years were included in each year's user count (i.e. included multiple times over the study period). These measures were adopted from previous published work on the prevalence of drug use (Aarts et al., 2014).

4.3.3.3 Incidence of study drug users

The annual incidence of study drug users was estimated from 2001 to 2015. Incidence cases were defined as patients with KOA who did not have the particular drug prescribed in the previous year, but thereafter. This was calculated for each study drug class by dividing the number of new users in the calendar year (numerator) by the total number of adult CPRD registrants at risk in the same year (denominator). The result was then multiplied by 1000 to calculate the incidence per 1000 CPRD registrants. The annual incidence was estimated from 2001 onwards, as data prior to that year (to be used to estimate the incidence rates in 2000) was not available.

4.3.3.4 Defined daily dose (DDD)

The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug for its main indication in adults. It is a standardised, technical unit of measurement created by the World Health Organisation (WHO, 2018). The measure of DDDs per 1000 CPRD registrants per day reflects the proportion of the population in primary care that, on average, receives the drug daily. It is considered a measure of the prevalence of drug

utilisation in a population (Zin et al., 2014). The mean annual DDD/1000 CPRD registrants was derived by calculating the total annual prescribed dose in milligrams for each drug, then dividing it by the DDD defined by the WHO Collaborating Centre and Drug Statistics Methodology (WHO, 2017). The result was then divided by the number of CPRD registrants each year, multiplied by 1000, and further divided by 365 to yield the annual number of DDDs/1000 CPRD registrants per day. The DDD of all individual drugs included in the study are presented in Table 4-1.

To quantify their utilisation, antidepressant drugs were grouped for analysis into four subclasses according to the major subclasses of antidepressants, as described in section 4.3 of the British National Formulary (BNF, 2014), namely: tricyclic and related antidepressants (TCAs subsection – 4.3.1), Monoamine Oxidase Inhibitors (MAOIs – subsection 4.3.2), Selective Serotonin Reuptake Inhibitors (SSRIs – subsection 4.3.3), and other antidepressants (subsection 4.3.4) (Table 4-1).

AEDs were grouped into two main groups: older AEDs and newer AEDs adopted from previous research publications (Italiano et al., 2015). The main difference between them is that the newer AEDs exhibit fewer pharmacokinetic drug–drug interactions, due to the absence of hepatic enzyme induction/inhibition properties. Newer AEDs also have fewer adverse drug events compared to older AEDs (Lee, 2014).

NSAIDs were also classified into two groups, non-selective NSAIDs and cyclooxygenase -2 (COX-2) inhibitors, depending on the isoenzyme they preferentially block. Non-selective NSAIDs inhibit both COX-1 and COX-2

indiscriminately, while COX-2 inhibitors selectively block the COX-2 isoenzyme. Based on their potency, opioids were classified into two groups: weak and strong opioids (Table 4-1 and 4-2). Prescriptions generated outside the uts period were excluded from further analysis.

Table 4-1 Study Drugs and Respective DDDs

	Drug Class and Subclasses	**Specific Drugs**	**DDD**	**Specific Drugs**	**DDD**
1.	**Antidepressants**				
	Tricyclic antidepressants (TCA)	Amitriptyline	75	Nortriptyline	75
		Imipramine	100	Doxepin	100
		Clomipramine	100	Dosulepin	150
		Lofepramine	105	Amoxapine	150
	Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine	20	Escitalopram	10
		Paroxetine	20	Sertraline	50
		Citalopram	20	Fluvoxamine	100
	Monoamine oxidase inhibitors (MAOIs)	Isocarboxazide	15	Meclobemide	300
		Phenelzine	60	Tranylcypromine	10
	Other antidepressants	Agomelatin	25	Mirtazapine	30
		Trazodone	300	Reboxetine	8
		Nefazodone	400	Mianserine	60
		Venlafaxine	100	Duloxetine	60
2.	**AEDs**				
	Older	Phenobarbital	100	Valproic acid	1500
		Ethosuximide	1250	Carbamazepine	1000
		Phenytoin	300	Clonazepam	8
		Primidone	1250		
	Newer	Levetiracetam	1500	Vigabatrin	2000
		Tiagabine	30	Pregabalin	300
		Lamotrigine	300	Lacosamide	300
		Gabapentin	1800	Rufinamide	1400
		Felbamate	2400	Zonisamide	200
		Oxcarbazepine	1000	Retigabine	900

Table 4-2 Study Drugs and Respective DDDs, continued

	Drug Class and Subclasses	Specific Drugs	DDD	Specific Drugs	DDD
3.	**NSAIDs**				
	Selective COX-2				
	Coxibs	Celecoxib	200	Etoricoxib	60
		Rofecoxib	25		
	Moderate COX-2 selective	Etodolac	400	Nemisulide	
	Oxicams	Meloxicam	15	Piroxicam	20
		Tenoxicam	20		
	Drugs with COX-1 & COX-2 activity				
		Diclofenac	100	Indomethacin	100
		Ibuprofen	1200	Nabumetone	1000
		Ketoprofen	150	Aceclofenac	200
		Dexibuprofen	800	Mefenamic acid	1000
		Dexketoprofen	75	Phenylbutazone	300
		Fenbufen	600	Fenoprofen	1200
		Tiaprofenic acid	600	Flurbiprofen	200
		Acemtacine	120	Naproxen	500
		Tolmetin	700	Ketorolac	30
4.	**Paracetamol**		3000		

DDD: defined daily doses in mg; AEDs: anti-epileptic drugs; COX: cyclooxygenase inhibitor, NSAID non-steroidal anti-inflammatory drugs

4.3.3.5 Oral Morphine Equivalent Doses (OMEQ) for Opioids

The calculation of this study measure involved several steps:

1. To drive the OMEQ doses per prescription, opioid dose was calculated by multiplying the strength in milligrams by the quantity prescribed for each prescription.

2. Opioid dose for each prescription (the result of step 1) was then multiplied by the published equianalgesic ratio (Svendsen et al., 2012), (FPM, 2019a), as summarised in Table 4-2.
3. The resulting OMEQ doses (the result of step 2) were summed up for each patient (i.e. OMEQ doses prescribed for individual prescriptions were summed up for each patient, within each year).
4. Finally, the total OMEQ dose per patient (the result of step 3) was divided by the total individual patient days of opioid supply per year (as detailed in section 4.3.5). This yielded the annual OMEQ dose per day of opioid supply within each year.

Patients with KOA were further classified according to the OMEQ dose per day into four dose ranks, ≤ 50, 51-≤100, 100 -200, and >200 mg OMEQ dose. These dose ranks reflect the intensity of exposure; previous research showed that patients receiving higher doses of opioids (≥100 mg/day) are more likely to deviate from the prescribed doses, using un-prescribed opioids or other substances that increase risk of overdose (Dunn et al., 2010). Additionally, the risk of harm increases substantially at doses above 120mg OMEQ per day without any increase in analgesic effects; hence, doses higher than a 120 mg OMEQ dose are considered high doses at which tapering or stopping opioids is recommended by the UK Faculty of Pain Medicine. Stratifying patients into low- and high-dose ranks will highlight patient groups that face a heightened risk of the harmful effects of opioids (e.g. overdose) according to their OMEQ dosing.

Table 4-3 List of Opioids, Corresponding DDD and Equianalgesic Ratios

Opioid Group	Drug	Route/Formulation	DDD	Equianalgesic Ratio
Stronger	Morphine	Oral	100	1
	Oxycodone	Oral	75	1.125
	Fentanyl	Transdermal	1.2	100
	Fentanyl	Transmucosal	0.6	50
	Tramadol	Oral	300	0.2
	Buprenorphine	Transdermal	1.2	100
	Buprenorphine	Sublingual	1.2	50
	Tapentadol	Oral	400	0.4
	Pethidine	Oral	400	0.1
	Hydromorphone	Oral	20	1.5
Weaker	Codeine	Oral	120	0.1
	Dihydrocodeine	Oral	150	0.13
	Dextropropoxyphene	Oral	140	0.15

DDD: defined daily dose; Equianalgesic ratio: potency of respective opioid or opioid formulation compared with oral morphine. Source: Svendson et al. (2012), and www.rcoa.ac.uk/faculty-of-pain-medicine/opioids

4.3.4 Days' Supply

The number of days' supply was calculated by dividing the quantity of each prescription by the numeric daily dose (NDD). The total days of supply for each patient per calendar year was derived from summing up all days of supply per prescription. Any overlapping days of supply between prescriptions were subtracted. This measure was calculated including prescriptions with complete data on NDD. Prescriptions with insufficient prescription information were excluded from the analysis of this study measure.

4.3.5 Data Management

A series of data checking steps were performed to ensure: valid gender and year of birth; first registration date (frd) at the practice was on or after birth date; current registration date (crd) was valid, on or after birth date, and on or after (frd); and the transfer out date was on or after (frd). Prescriptions were included if the prescription date was on or after the uts date.

4.3.6 Data Analysis

Patients with a diagnosis of KOA were stratified according to the prescribed drug class (antidepressants, AEDs, opioids, NSAIDs and paracetamol) into five groups, and the number of patients prescribed each class was determined on an annual basis between the years 2000 and 2015.

The annual number of prescriptions of each of the study drug classes was also reported as the number of prescriptions per 1000 CPRD registrants and was plotted over the study period to visually describe prescribing prevalence. The prevalence and incidence rates of study drug users were reported per 1000 CPRD registrants. The percentage change in drug utilisation measures was observed on an annual basis between 2000 and 2015, and data for each variable was reported.

4.4 Results

4.4.1 Number of Prescriptions

In total there were 9,259,496 prescriptions of the five study drug classes, prescribed for 117,637 patients with KOA during the 16-year study period. The number of prescriptions issued for patients with KOA over the study period varied according to the drug class, ranging from just over half a million prescriptions of AEDs (n=520,844) to more than 3 million prescriptions of opioids (n=3,230,198) (Table 4-3).

Overall, opioids were the most frequently prescribed class with 3,230,198 (34.9%) prescriptions, followed by paracetamol with 2,135,814 (23.1%) prescriptions, antidepressants with 2,054,261 (22.2%), NSAIDs with 1,318,379 (14.2%) and AEDs with 520,844 (5.6%). The number of prescriptions per 1000 CPRD registrants showed an overall increase over the study period for all classes (which peaked at 2014) except NSAIDs, as presented in Table 4-3 and Figure 4-1.

The most prominent increase in number of prescriptions per 1000 registrants was for AED use, where an increase of 346.1% was found in 2014 compared to 2000 (from 2 prescriptions per 1000 registrants in 2000 to 11 prescriptions per 1000 registrants in 2014), followed by antidepressants, with an increase of 152.8% (from 14 in 2000 to 35 prescriptions per 1000 registrants in 2014).

Table 4-4 Number of Prescriptions During Study Period

Study Drug Class	Total no. Prescriptions During Follow-up	Number of Prescriptions per 1000 CPRD Registrants		% Change between 2000 and 2014
		2000	2014	
Antidepressants	2,054,261	14.0	35.4	152.8(+)
AEDs	520,844	2.6	11.6	346.1(+)
Opioids	3,230,198	27.5	46.5	69.0 (+)
NSAIDs	1,318,379	17.5	7.4	57.7(-)
Paracetamol	2,135,814	20.5	31.2	52.2(+)

AEDs: anti-epileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; (+) % increase (-) % decrease

Opioids were the most frequently prescribed drug class with the highest number of prescriptions per 1000 registrants in every study year and had increased from 27 to 46 prescriptions per 1000 registrants, and by 69.0%, from 2000 to 2014 (Figure 4-1). There was an observed overall drop in the number of prescriptions across studied drug classes in 2015, with opioid to 28.7, antidepressants to 22.7 AEDs to 7.5 paracetamol to 19.0 NSAID to 4.2 prescriptions per 1000 CPRD registrants. However, it was not possible to confirm any trend of this drop with data from subsequent years as the study ended in 2015.

The trend of NSAID prescriptions showed an increase from 2000 to 2004, with the number of prescriptions increasing from 17 to 24 prescriptions per 1000 CPRD registrants. However, this was followed by a gradual decline from 2004 onwards, and from 2000 to 2015 the number of NSAID prescriptions per 1000 CPRD registrants dropped from 17 to 4 (57.7% drop).

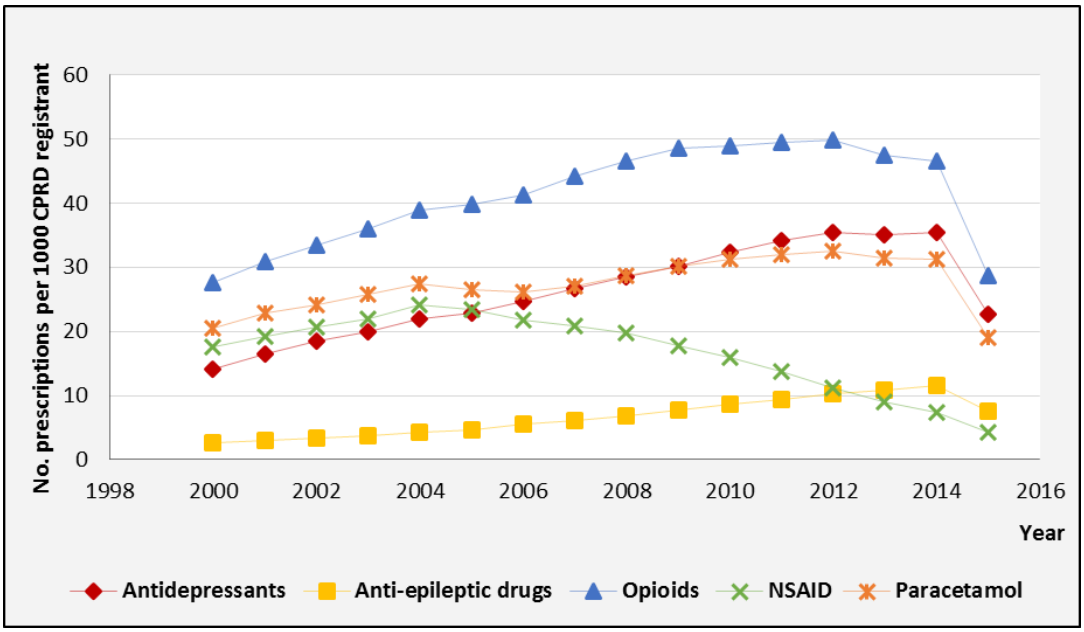


Figure 4-1 Number of Prescriptions per 1000 CPRD Registrants.

4.4.2 Prevalence of Study Drug Users

Overall, 93,007 (79.0%) of patients diagnosed with KOA (n= 117,637) used opioids during follow-up, followed by NSAIDs used by 84,750 (72.0%) patients, paracetamol used by 82,497 (70.1%), antidepressants by 53,467 (45.4%), and AEDs used by 15,814 (13.4%) of the total patients diagnosed with KOA.

Consistent with the trends of prescriptions per 1000 CPRD registrants, the prevalence of study class users (measured as number of patients per 1000 CPRD registrants) showed an overall increase for all classes except NSAIDs, where a decline following 2004 was observed. Changes in the prevalence of study class users are shown in Table 4-4.

Table 4-5 Number Prescribed Respective Drug Class and % Change Over Time

Study Drug Class	Total no. Patients Prescribed	Number of Patients Prescribed Respective Drug Class per 1000 CPRD Registrants		% Change Between 2000 & 2014
		2000	2014	
Antidepressants	53,467	2.4	3.7	54.0% (+)
AEDs	15,814	0.3	1.2	300.0% (+)
Opioids	93,007	5.3	6.5	22.6% (+)
NSAIDs	84,750	5.0	1.8	64.0% (-)
Paracetamol	82,497	4.4	5.4	22.7% (+)

AEDs: anti-epileptic drugs; NSAIDs: Non-steroidal anti-inflammatory drugs; (+) % increase (-) % decrease

A continuous and steady increase in the number of patients who were prescribed AEDs and opioids was observed throughout the study years. However, the number of patients prescribed opioids decreased during 2013 and 2014 (from 5 patients in 2000, plateaued at 7 from 2010 to 2012, and dropped to 6 in 2013 to 2014) (Figure 4-2).

Opioids were the most frequently prescribed drug class in every study year, and the number of patients per 1000 CPRD registrants was the highest compared to other drug classes (in 2000, 5 patients were prescribed opioids vs 4, 2 and 0 per 1000 CPRD registrants prescribed paracetamol, antidepressants and AEDs, respectively; in 2015, 5 patients were prescribed opioids vs 4, 3, 1 and 1 per 1000 CPRD registrants prescribed paracetamol, antidepressants, NSAIDs and AEDs) (Figure 4-2).

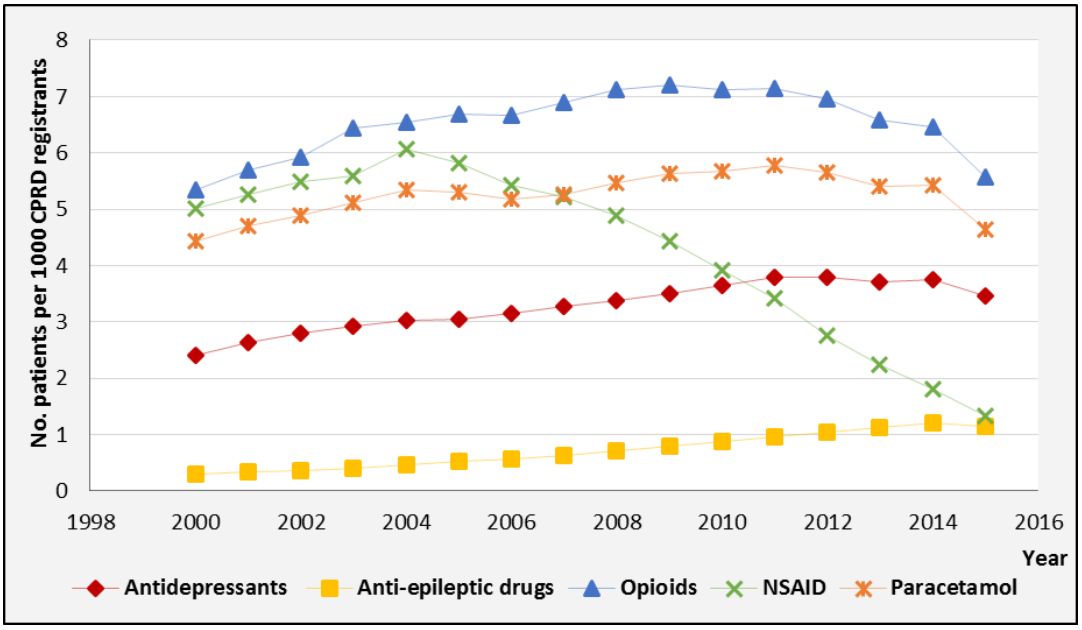


Figure 4-2 Number of Patients per 1000 Registrants by Study Drug Class.

The number of patients who were prescribed antidepressants showed a continuous increase from 2000 to 2011, and remained stable between 2011 and 2014, before a slight drop in 2015 (from 2000 to 2015, the figure changed from 2 to 3 patients per 1000 CPRD registrants). There was a decline in the prevalence of NSAID users from 2005 onwards, whilst the prevalence of paracetamol users showed a slight increase from 4.4 users per 1000 CPRD registrants to 5.4 and 4.6 users per 1000 CPRD registrants in 2014 and 2015, respectively.

4.4.3 Incidence of Study Drug Users

The annual number of new users within each class measured per 1000 CPRD registrants showed a decreasing trend throughout the course of study. This was true for all drug classes apart from AEDs, where the trend in new users was increasing (Figure 4-3).

Over the study period, the number of new antidepressant and opioid users per 1000 CPRD registrants halved (from 1 to 0.5 and from 2 to 1, respectively), while new paracetamol users dropped from 1.7 to 1.3 over the same period (23% decrease). An increase in the number of new NSAID users from 2001 to 2004 was observed, followed by a sharp decline thereafter; the number of new users per year between 2004 and 2015 was 2.5 and 0.4 patients per 1000 CPRD registrants.

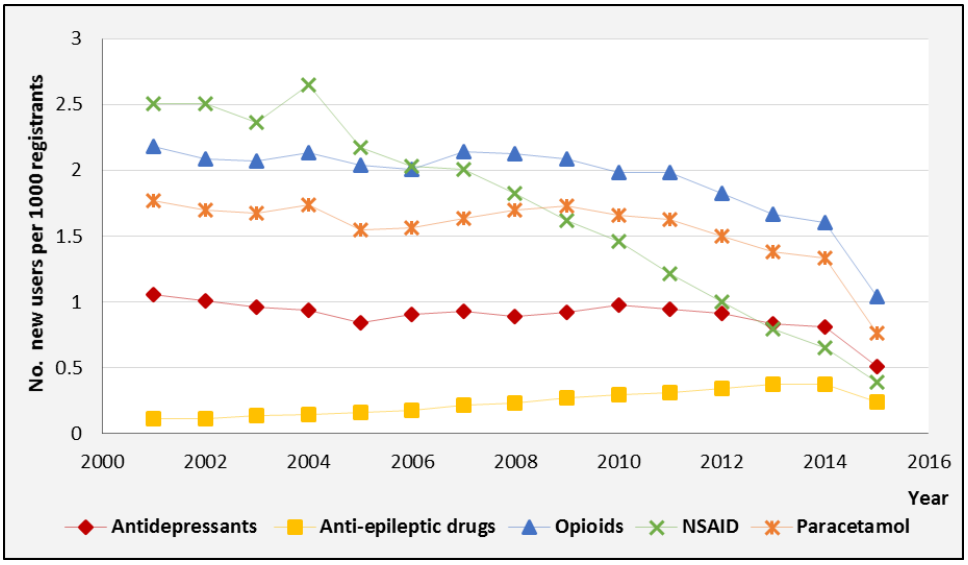


Figure 4-3 Number of New Users of Respective Drug Classes

On the contrary, the number of patients newly initiating AEDs tripled from 0.1 patients per 1000 CPRD registrants in 2000, to 0.3 in 2014, and to 0.2 in 2015 (Figure 4-3).

4.4.4 Mean Number of Prescriptions per Patient per Year

The mean number of antidepressants, AED and opioid prescriptions per patient per year showed a gradual increase between 2000 and 2015, from 5.8 to 9.6, 8.7 to 9.6 and 5.1 to 7.2, respectively, representing 65.5%, 10.3% and 41.1% increases, respectively. The annual number of prescriptions per patient per year for NSAIDs and paracetamol remained stable over the study period, ranging from 3 to 4 and 4 to 5 prescriptions, respectively (Figure 4-4).

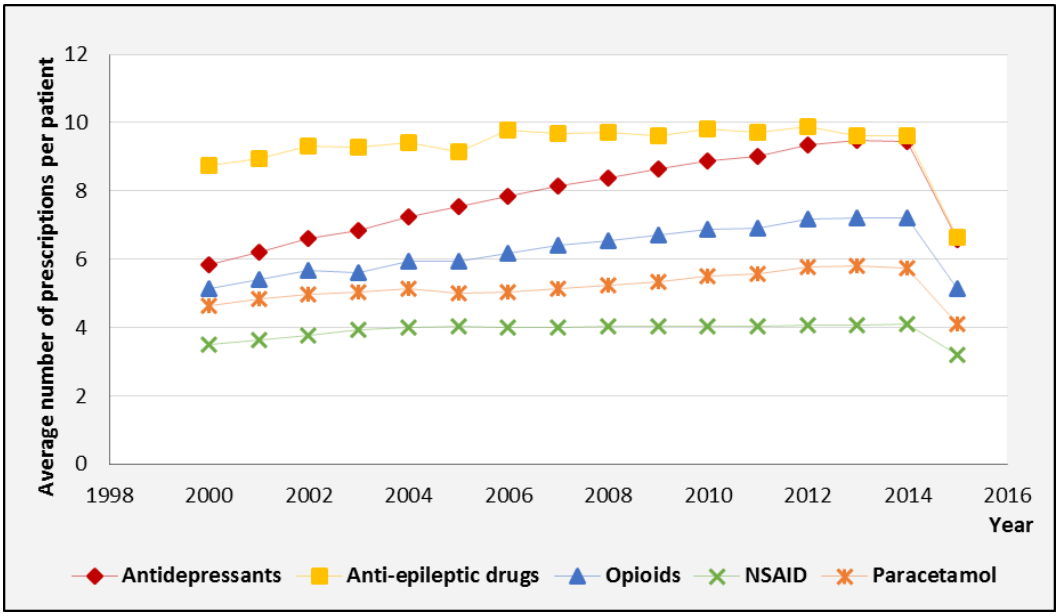
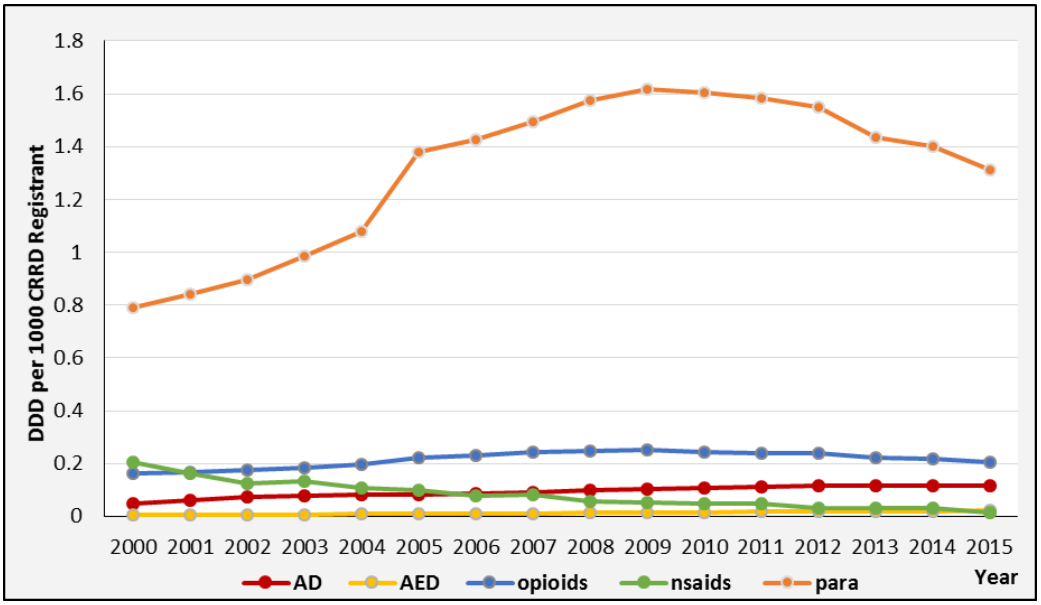


Figure 4-4 Mean Number of Prescriptions per Patient per Year.

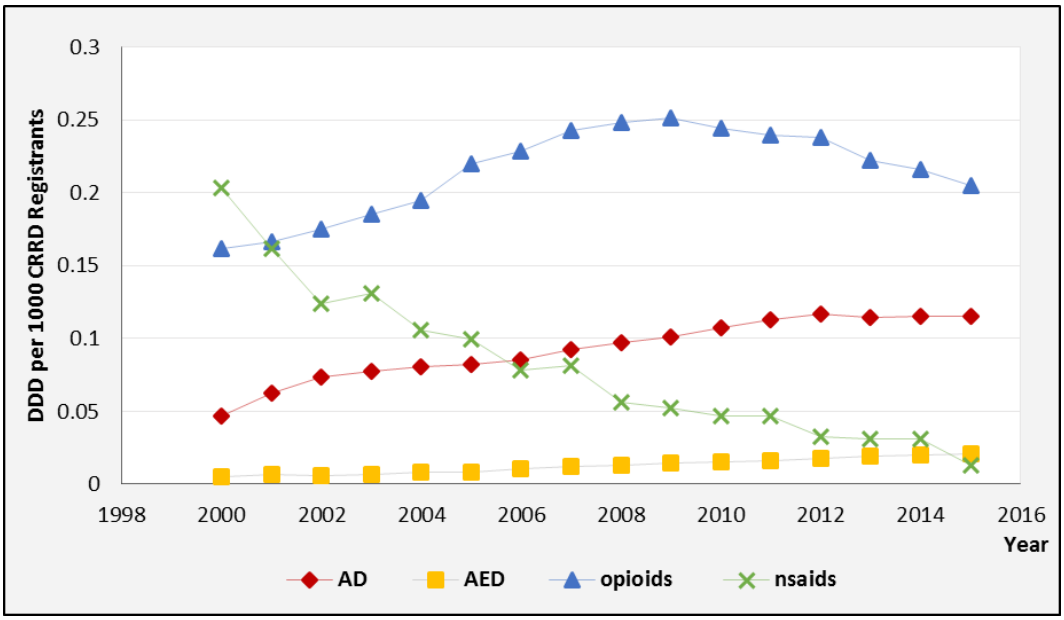
4.4.5 Defined daily doses (DDD) of Study Drug Classes

During the study period, the mean number of DDDs per day for paracetamol increased from 0.8 in 2000 to peak at 1.6 in 2009, before a gradual decrease between the years 2011 and 2015 (from 1.5 to 1.3 DDDs per 1000 CPRD registrants), as illustrated in Figure 4-5.



AD Antidepressants AED anti-epileptic drug nsaids Non-steroidal anti-inflammatory drugs para paracetamol

Figure 4-5 Mean Number of DDD per 1000 Registrants, all Study Drug Classes.



AD Antidepressants AED anti-epileptic drug nsaids Non-steroidal anti-inflammatory drugs

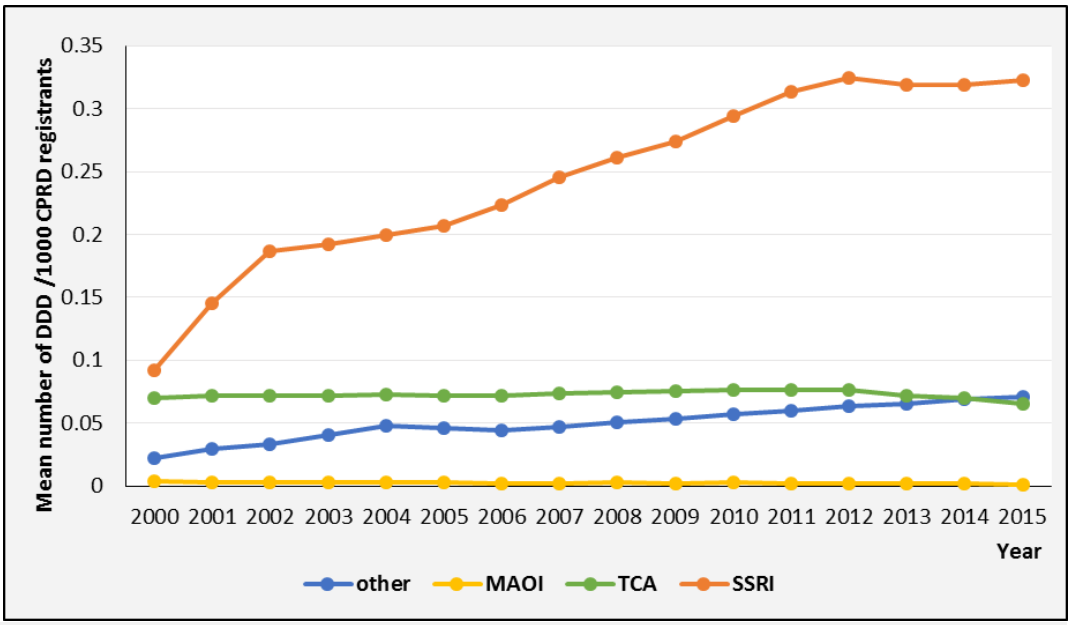
Figure 4-6 Mean Annual DDD per 1000 CPRD Registrants (excluding paracetamol)

The mean DDDs per 1000 registrants per day showed varying trends; for antidepressants, AEDs and opioids, DDD per 1000 CPRD registrants per day increased, whereas for NSAIDs they continuously declined over the study years (Figure 4-6). Opioids were prescribed at a higher number of DDDs per day compared to antidepressants, AEDs and NSAIDs throughout the 16-year study period (Figure 4-6). The number of opioid DDDs per day increased from 2000 to 2012 and was stable thereafter.

In the subsequent sections, details on the DDDs of individual study drug classes are included.

4.4.5.1 Defined daily doses of Antidepressant Subclasses

Several distinctive patterns were observed within individual antidepressant classes, as demonstrated in Figure 4-7. There was a gradual increase in the number of DDD/1000 registrants per day for TCAs, which peaked at 0.077 DDDs in 2012, followed by a rather sharp decrease thereafter. The number of DDDs per 1000 registrants for SSRIs and other antidepressant subclasses increased throughout the study period, from 0.09 to 0.32 and from 0.02 to 0.06 DDDs per patient per day (from 2000 to 2015) for SSRIs and other antidepressants, respectively. The trend for MAO inhibitors declined over the study years, from 0.003 to 0.001 DDD/1000 registrants (from 2000 to 2015).



TCA Tricyclic Antidepressants, SSRI Selective Serotonin Reputable Inhibitors, MAOI Monoamine Oxidase Inhibitors

Figure 4-7 Mean DDD/1000 CPRD Registrants for Antidepressants by Subclasses.

4.4.5.2 Defined Daily Doses of AEDs

For AEDs, the mean DDD per 1000 registrants per day varied considerably between older and newer agents. For older AEDs, the mean annual DDD per 1000 CPRD registrants was stable until 2013 but decreased over the final two study years (2014–15) (Figure 4-8). On the contrary, the mean annual DDD per 1000 CPRD registrants for newer AEDs had shown a dramatic and sharp rise over the study period (from 0.009 DDD/1000 registrants in 2000 to 0.0267 DDD/1000 registrants in 2015 – a 300% increase over the study period).

In a more detailed analysis of the newer AEDs, the prescribing of gabapentin and pregabalin increased more than for other specific drugs. Pregabalin utilisation started in 2004, and has since demonstrated a

continuous increase along with gabapentin, from 0.035 to 0.270 DDD/1000 CPRD registrants (671% increase) (Figures.4-9 and 4-10).

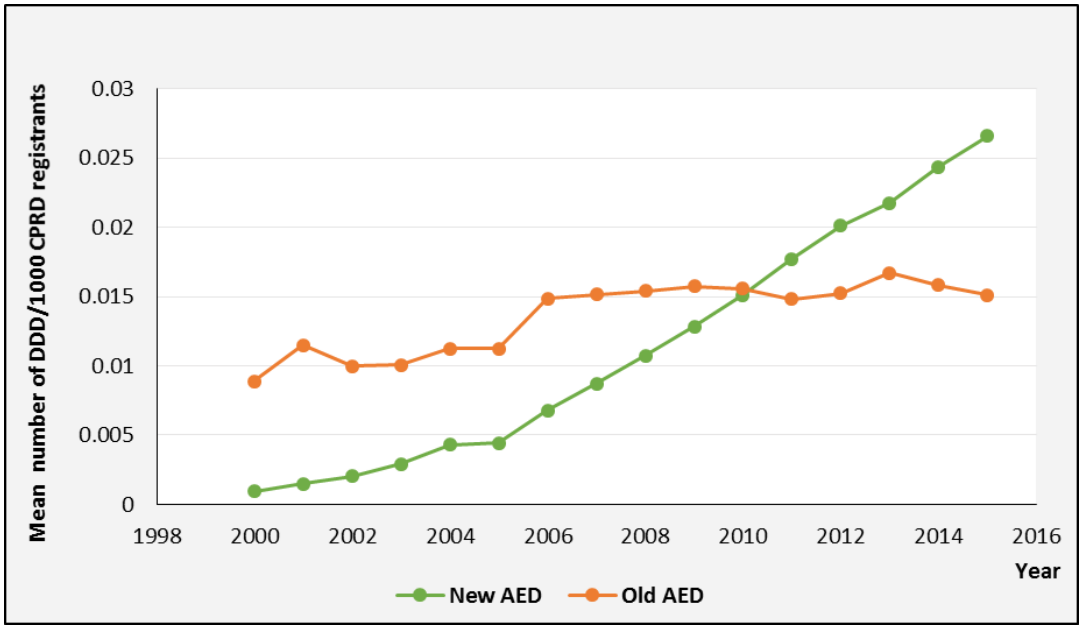


Figure 4-8 Mean Annual DDD/1000 CPRD Registrants for Drugs AEDs.

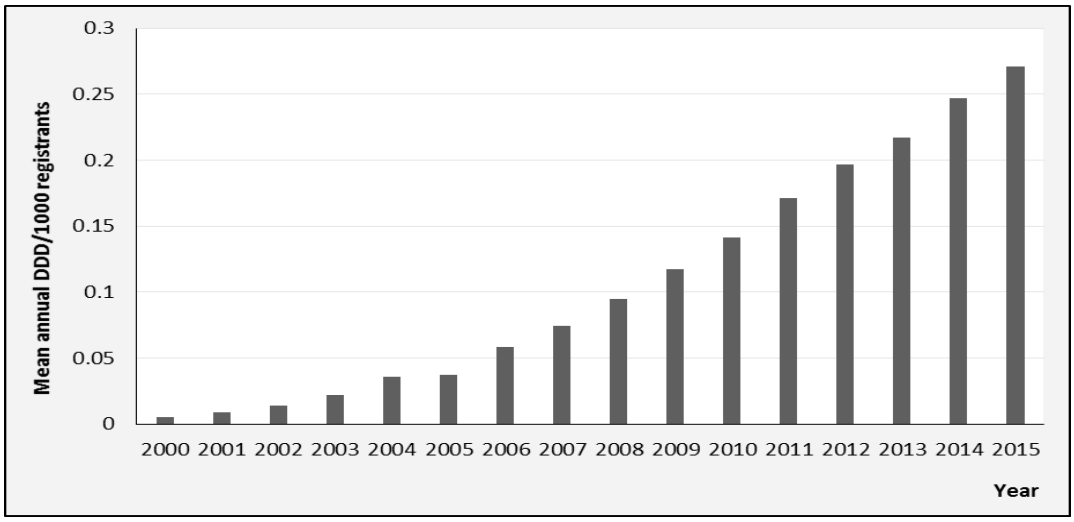


Figure 4-9 Mean annual DDD per 1000 CPRD registrants for gabapentinoids.

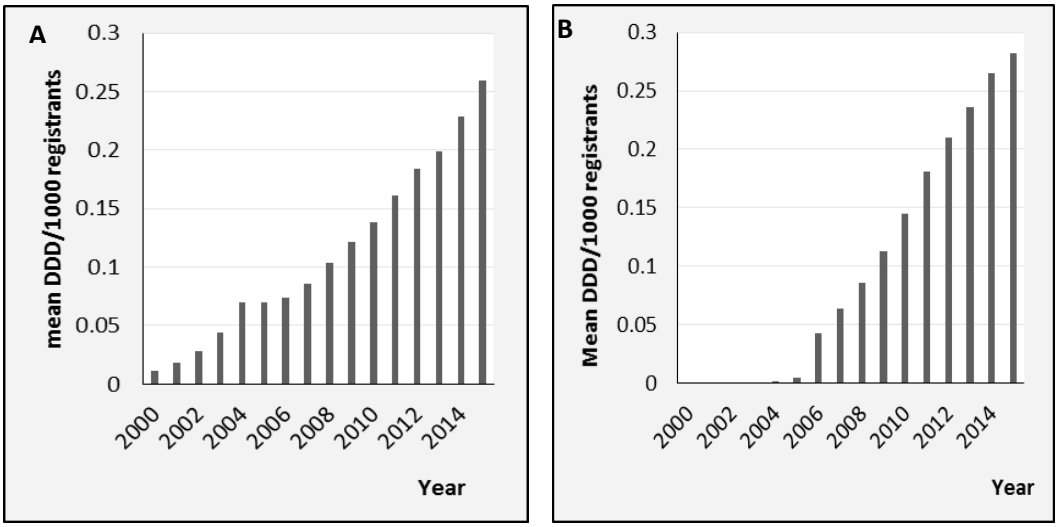


Figure 4-10 Mean DDD per 1000 registrants-of (A) gabapentin and (B) pregabalin.

4.4.5.3 Defined Daily Doses of Opioids

There was an overall increase in the mean number of DDD per 1000 registrants during the study years; however, the most prominent change was in the number of DDDs of tramadol, which increased from 0.11 DDDs in 2000 to 0.64 DDDs per 1000 registrants per day in 2015 (Figure 4-11). Within strong opioids, an increase in prescribing prevalence of morphine and oxycodone was also prominent, with an increase from 0.01 to 0.1 for morphine, and an increase from 0.006 to 0.06 DDDs per 1000 registrants per day for oxycodone from 2000 to 2015 (Figure 4-11).

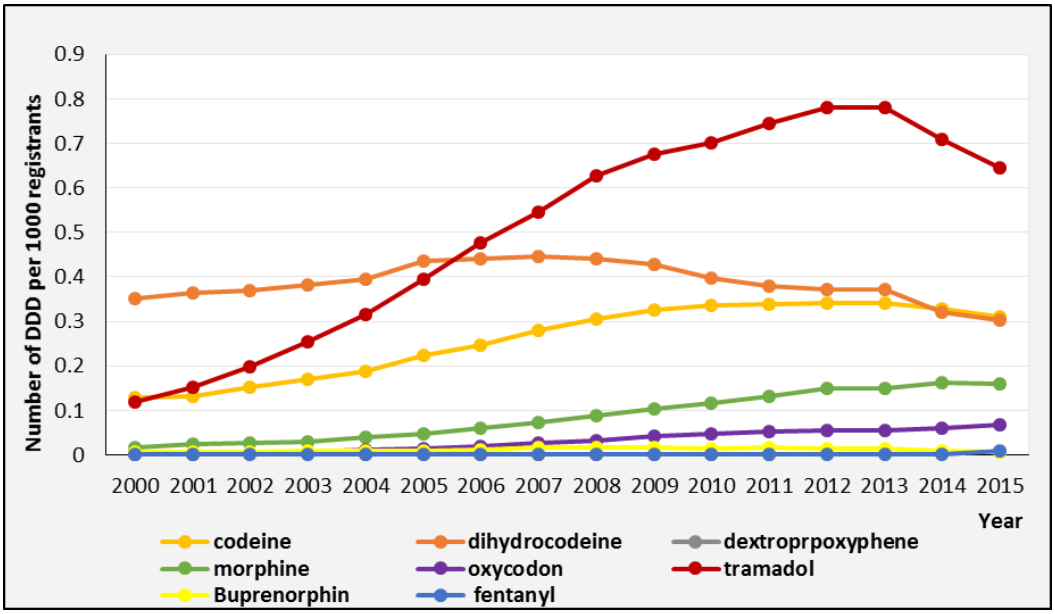


Figure 4-10 Mean Number of DDDs per 1000 CPRD Registrants for Opioids.

The mean number of DDDs per 1000 registrants for codeine showed a steady increase from 2000 to 2013, from 0.12 to 0.34. However, after 2013, a slight drop was seen, to 0.30 in 2015 (Figure 4-11). Similarly, a drop in the prevalence of dihydrocodeine was also observed during 2014 and 2015.

A slight peak was observed in the number of DDDs of dihydrocodeine in 2005 (from 0.39 DDD to 0.43 DDD per 1000 registrants, from 2004 to 2005), along with a continued rise in codeine DDDs from 2004 to 2013 (Figure 4-11). When both strong and weak opioids were analysed simultaneously, it was observed that dihydrocodeine was the most prevalent opioid over the early years of the study (from 2000 to 2005). However, tramadol became the most prevalent individual opioid thereafter, with a sharp increase in the number of DDDs per 1000 registrants per day from 2004 to 2013 – from 0.31 to 0.78 DDDs per 1000 registrants per day (151.6% increase).

4.4.5.4 Defined Daily Doses of NSAIDs

Selective COX-2 inhibitors increased sharply over the period from 2000 to 2005 (from 0.002 to 0.009 DDD/1000 registrants, 350% increase), but declined slowly until 2008 (from 0.009 in 2005 to 0.0085 DDD per 1000 registrants in 2008, 5.5% decrease), and more rapidly thereafter. Non-selective NSAIDs declined throughout.

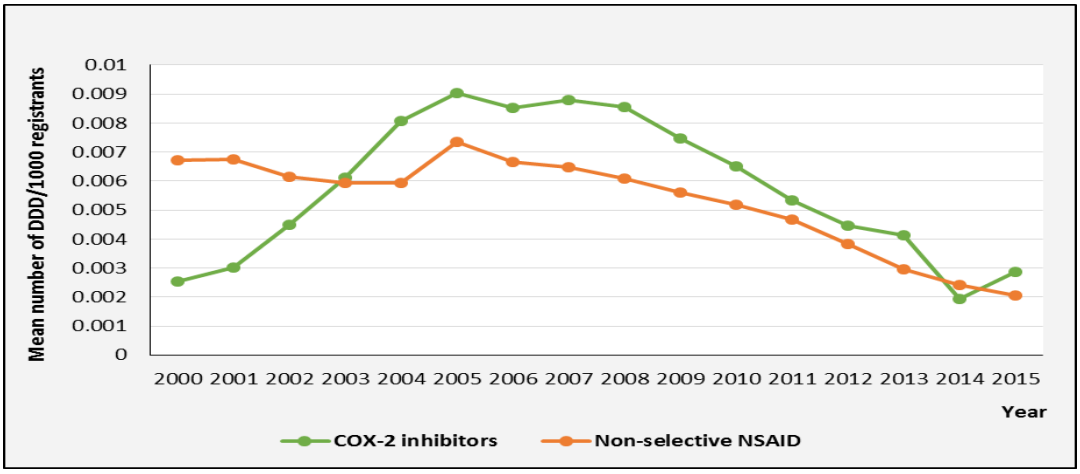


Figure 4-11 Mean Annual DDD per 1000 CPRD Registrants for NSAIDs.

4.4.6 Annual Number of OMEQ Doses

Over the study period, the annual OMEQ per 1000 CPRD registrants per day increased from 32.6 mg (in 2000) to peak at 76.0 mg in 2012 (133% increase), before decreasing thereafter to 71.7 mg in 2014 and 43.6 mg in 2015 (representing 119.9% and 33.7% increases in 2014 and 2015, respectively, from 2000) (Figure 4-13).

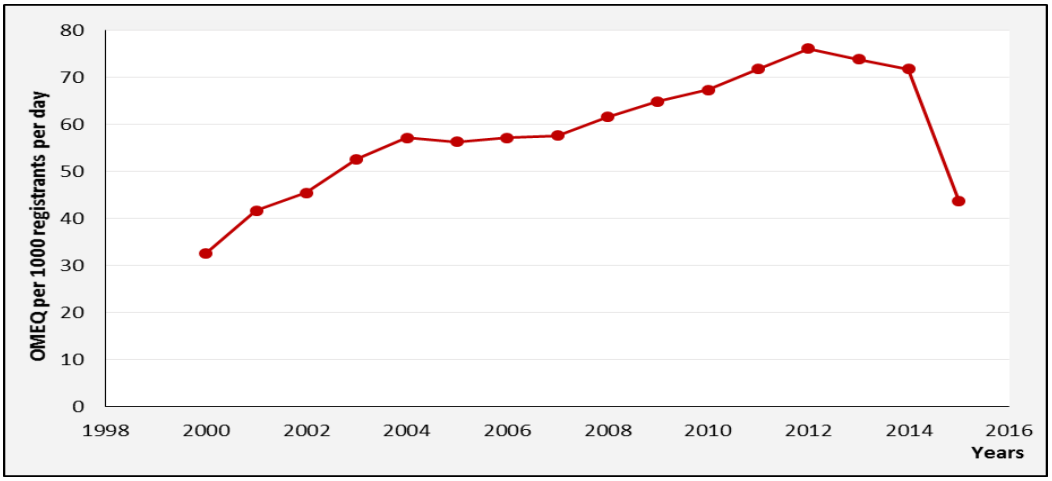


Figure 4-12 Mean Number of Oral Morphine Equivalent (OMEQ) Dose per 1000 Registrants per Day.

There was a gradual increase in the number of patients with KOA who used ≤50 mg OMEQ doses during the study years; however, a drop was observed over time, particularly during 2014 and 2015 (Figure 4-14). On the other hand, there was a continuous rise in the proportion of patients who used higher OMEQ doses (≥50mg), including those who used 100 to 200mg and >200mg OMEQ per day.

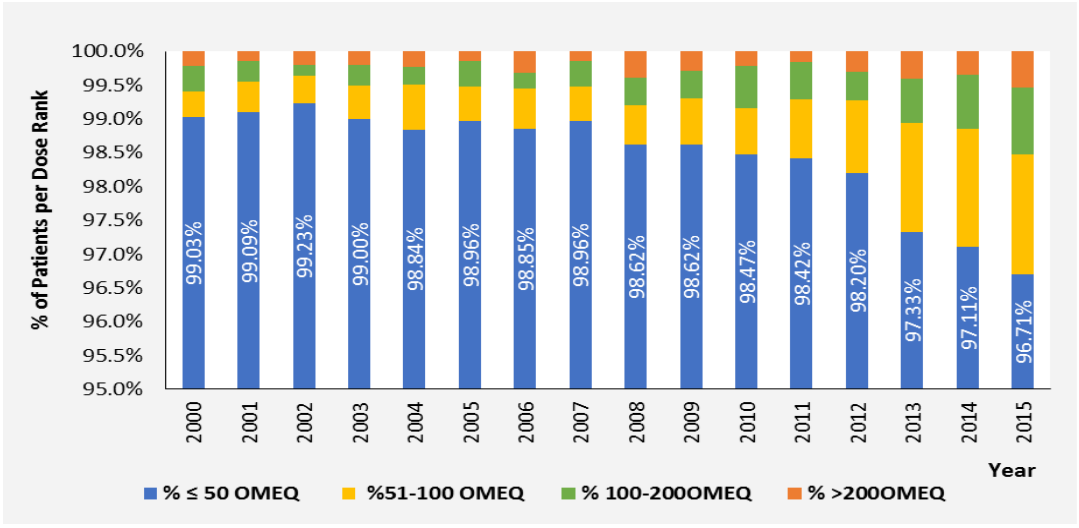


Figure 4-13 Proportion of Patients with Respective Oral Morphine Equivalent (OMEQ) Dose per Day by Study Year.

4.4.7 Days' Supply

4.4.7.1 Proportion of Included Prescriptions

Prescriptions with complete information were included in the analysis of this study measure. The proportion of prescriptions with insufficient information to calculate the days' supply were excluded (Table 4-5).

Table 4-6 Proportion of Prescriptions Excluded from Estimates of Days' Supply

Drug class	Total Prescriptions	No. Prescriptions with Insufficient Info to Calculate Days' Supply (% From Total in Class)
Antidepressants	2,054,261	264,652 (12.8)
AEDs	520,844	142,565(27.3)
Opioids	3,230,198	756,135 (23.4)
NSAIDs	1,318,379	109,990 (8.3)
Paracetamol	2,135,814	345,265(16.1)

4.4.7.2 Results on Days' Supply

An increase in the mean number of antidepressant and NSAID days' supply was observed over the study years, from 167.2 (SD 129.3) days in 2000 to 200.8 (SD 143.7) in 2012 for antidepressants, and from 158.7 (SD 129.0) in 2000 to 196.7 (SD 144.3) in 2012 for NSAIDs (20% and 24% increases, respectively). However, this was followed by a decrease from 186.5 (SD143.5) to 179.0 (SD 138.4) days per year for antidepressants and NSAIDs, respectively, from 2013 to 2015. Over the study period, the duration of therapy each year for AEDs decreased slowly from 91.1 (SD 100.1) days to 71.5 (SD 89.1) days from 2000 to 2015, while paracetamol slightly increased from 55.7 (SD 78.9) in 2000 to 67.2 (SD 91.6) days in 2015. The mean annual days of supply of opioids showed an overall increase from 66.9 (SD 92.6) days in 2000 until 2010, peaking at 96.1 (SD

90.1) days (43.6% increase). However, this was followed by a decline in the number of days over the last years of the study to 82.8 (SD 112.6) days in 2015 (13.3% decrease from 2010 to 2015).

A summary of changes in study measures between the years 2000 and 2015 is in Table 4-6.

Table 4-7 Summary of Change in Study Measures During the Study Years (%)

Study measures	**Antidepr-essants**	**AEDs**	**Opioids**	**NSAIDs**	**Paraceta-mol**
Total prescriptions	2,054,261	520,844	3,230,198	1,318,379	2,135,814
prescriptions per1000 CPRD registrants	152.8 (+)	346.1 (+)	69.0 (+)	57.7 (-)	52.2 (+)
respective drug class users per 1000 registrants	54.0 (+)	300.0 (+)	22.6 (+)	64.0 (-)	22.7 (+)
new users of respective class per 1000 registrants	51.5 (-)	100 (+)	54.3 (-)	84.5 (-)	56.8 (-)
Mean prescriptions/patient / year	58.0 (+)	12.5 (+)	53.2 (+)	57.1 (+)	27.2 (+)
Mean annual days' supply	7.9 (+)	21.5 (-)	23.8 (+)	12.7 (+)	20.6 (+)

(+) percentage increase over the study period (-) percentage decrease over the study period

4.5 Discussion

4.5.1 Main Findings

This cross-sectional study identified an overall increase in the prescribing of antidepressants, AEDs, opioids and paracetamol in patients with KOA in the UK primary care setting between 2000 and 2015. The most prominent increase was found in AED prescribing, where the number of prescriptions increased from 2 to 11 per 1000 CPRD registrants, and the number of AED users increased from 3 to 12 users per 10,000 CPRD registrants (from 2000 to 2014, respectively).

Opioids were the most frequently prescribed class, and within opioids, tramadol was the most frequently prescribed single agent, for which the DDD per 1000 CPRD registrants increased from 0.11 to 0.64 in 2000 to 2015, respectively.

The study also found an overall decrease in the number of prescriptions and patients prescribed NSAIDs between 2004 and 2015, with the numbers dropping from 17.5 to 7.4 and 5.0 to 1.8 for prescriptions and patients per 1000 CPRD registrants, respectively.

In the following subsections, findings from the present study were compared with drug utilisation studies of patients with OA/KOA (subsection 4.5.2). Additionally, findings were compared with results from studies on the utilisation of individual drug classes for different conditions or populations (subsection 4.5.3).

4.5.2 Comparison with Other Studies of Patients with OA/KOA

4.5.2.1 Comparisons with Findings on Opioid Utilisation in Patients with OA/KOA

The present study found an overall increase in the utilisation of opioids, which was in line with findings reported by previous UK and international studies. In the UK, Yu et al. (2017) reported an increase in opioid prescriptions from 0.1% to 1.9% in patients with a new OA diagnosis between 1993 and 2013 (n=733 and 25,145 patients in 1993 and 2013, respectively) (Yu et al., 2017). Similarly, a significant increase of 29% in opioid prescribing was found in the US in a sample of 1,387 Medicare Current Beneficiary Survey participants between 2003 and 2009 (Wright et al., 2014). A total of 31% of patients with KOA received opioids in 2003 compared to 40% in 2009 (OR 1.5, 95% CI 1.1, 2.0 for 2006 and 2009 compared to 2003) (Wright et al., 2014). Additionally, the proportion of opioid users in a cohort of Australian patients with KOA during the year prior to total knee replacement (TKR) increased from 37.4% to 48.6% ($p<0.0001$) from 2001 to 2012 (n=1,205 and 1,087) (Inacio et al., 2018).

However, the number of incident users of opioids reported in the present study declined over time (from 2.1 to 1.0 per 1000 CPRD registrants from 2000 to 2015). This contrasted with the finding reported by Wilson et al. (2015), who measured incident opioid use in new cases of OA and reported an increase of 26%. The study found that incident users of opioids among new OA cases significantly increased from 2006 to 2010, from 15.3 per 100

person-years (99% CI 14.5, 16.1) to 19.3 per 100 person-years (99% CI 18.3, 20.5) (Wilson et al., 2015).

The difference in findings could possibly be explained by the fact that Wilson et al. (2014) included patients with OA of any joint, hence the increase in new opioid users could have stemmed from the increased incidence of OA patients, for whom opioids were initiated during the respective years. However, the present study included only patients with KOA, and reported a stable incidence of KOA diagnosis in CPRD between 2000 and 2015 (as presented in Chapter 3). The decrease in the incidence of opioid users over time could also be a result of the widespread awareness among general practitioners of opioid harm reported through research findings, or it may also indicate better adherence to clinical guidelines, which recommend opioids as a second- or third-line therapy in patients with OA (Conaghan et al., 2008).

The present study found a gradual increase in the proportion of patients using higher OMEQ dose ranks, which can be possibly interpreted as an increased proportion of strong opioid users within the cohort. This was also the finding reported by a previous study, where the proportion of patients using very strong opioids rose from 0.1 to 1.2 per 100 patients with OA diagnosis, and the proportion of strong opioid users doubled from 0.1 to 0.2 per 100 patients with OA diagnosis from 1993 to 2013 (Yu et al., 2017).

4.5.2.2 Comparisons with studies on NSAID utilisation in patients with OA/KOA

The present study found an overall decrease in the prescribing of NSAIDs during the study period. The finding is consistent with that reported by Yu et al. (2017), where COX-2 users dropped from 12.1% to 0.6%, and NSAID users from 27% to 12.5%, from 2004 and 2013 (Yu et al., 2017). Similar to the UK, a study from the US also reported a decrease in NSAID prescriptions, with a drop from 41% to 31% from 2003 to 2009, using an administrative database (n= 1,387) (Wright et al., 2014). Additionally, the prevalence of prescriptions of NSAID decreased from 76% to 50.3% from 2001 to 2012, as reported in patients waiting for TKR in Australia (n=1,205 and 1,087, respectively) (Inacio et al., 2018).

The overall decrease in the prescribing of NSAIDs in the present study could be explained by the influence of national advice and guidelines. In 2004 the Medicine and Healthcare product Regulatory Agency (MHRA) issued a safety directive advising the avoidance of COX-2 inhibitors, due to increased risk of cardiovascular side effects such as myocardial infarction and stroke (MHRA, 2004). The directive was further extended to include cautionary use of non-selective NSAIDs, due to increased risk of thrombotic events, and all prescribers were advised to keep doses to the minimum effective level, and to tailor doses according to patients' risk profiles (MHRA, 2005a, MHRA, 2005b). The impact of MHRA guidance on GPs' prescribing activities was studied by examining the trends of analgesic prescribing prior to and following the safety advice on NSAIDs (Bedson et al., 2013). There was a

rapid decrease in the proportion of patients being newly prescribed COX-2 and NSAIDs following the issuance of this MHRA guidance (Bedson et al., 2013). Furthermore, the drop in the mean annual DDD of NSAIDs per 1000 CPRD registrants found in the present study possibly indicates better adherence to management guidelines, which have recommended the use of NSAIDs at the lowest possible dose and after consideration of an individual patient's risk profile (NICE, 2008).

4.5.2.3 Comparison with studies on paracetamol use in patients with OA/KOA

The present study reported an increase in the prescriptions of paracetamol, which was consistent with findings on analgesic use one year prior to TKR. The study found that the overall prevalence of paracetamol prescriptions increased from 52.1% to 61.4% over the period of 2001 to 2012 in Australia (total number of patients: 1,257 and 1,113 in 2001 and 2012, respectively) (Inacio et al., 2018).

4.5.2.4 Comparison with studies on use of AEDs in patients with OA/KOA

The present study found an overall increase in AED prescribing, which was largely due to the increased utilisation of gabapentinoids. This was consistent with findings from a recent population-based study using data from the CPRD (Appleyard et al., 2019). The study found a substantial rise

in the incidence of gabapentinoid prescribing from 9.5 (95% CI: 9.0, 10.1) to 28.0 (27.2, 28.8) first prescriptions per 1000 person-years from 2005 to 2014, representing a three-fold increase.

4.5.3 Comparison with Other Studies of Individual Drug Class Prescribing Prevalence

In this section, the results from the present study were compared to those from studies which described the utilisation of individual drug classes in conditions or populations other than OA/KOA.

4.5.3.1 Antidepressants

The increase in antidepressant prescribing over time found in the present study was consistent with findings reported in several population-based studies (Mars et al., 2017), (Noordam et al., 2015), (Aarts et al., 2014). In the UK, the number of antidepressant prescriptions rose from 61.9 per 1000 person-years (PY) in 1995 to 129.9 per 1000 PY in 2011 (Mars et al., 2017). The study included 1,280,995 prescriptions for 350,398 registrants within the CPRD. Similarly, antidepressant prevalence increased from 3.9% in 1991 to 8.3% in 2011 in a study in Rotterdam including 14,926 patients who received 89,622 prescriptions (Aarts et al., 2014). Additionally, a different study reported increased antidepressant prescribing prevalence from 35.5 per 1000 patients in 1996 to 69.8 per 1000 patients in 2012 (Noordam et al., 2015). These population-based studies included patients who were

prescribed antidepressants at least once during the respective study periods, regardless of the indication. This implies the inclusion of patients with KOA within the studied general population of the above studies by Mars et al. (2017), Aarts et al. (2014) and Noordam et al. (2015). However, the magnitude of the overall increase in the number of prescriptions between 2000 and 2014 was 152.8% in the present study, whereas that reported by Mars et al. was 109.8%. This may possibly indicate a greater change in antidepressant prescribing prevalence within the population of KOA compared to the population in general.

The increased prevalence of antidepressant prescribing was also reported in patients with diagnosed depression or anxiety and sleep disorders. In the UK, the average number of prescriptions issued per patient increased from 2.8 in 1993 to 5.6 in 2004 (Moore et al., 2009). Additionally, the number of patients prescribed antidepressants increased from 836 per 10,000 PY in 2001 to 913 per 10,000 PY in 2009 (Abbing-Karahagopian et al., 2014). These population-based studies in patients with diagnosed depression/anxiety disorders probably included the subset of patients with KOA, who were also diagnosed with depression, anxiety or sleep disorders.

Consistent with the present study's findings of an increase in antidepressant DDDs per 1000 CPRD registrants (from 0.04 to 0.11 DDDs/1000 registrants from 2000 to 2015, representing a three-fold increase), research using sales data showed a 44% increase from 30.3 DDDs/1000 inhabitants per day in 2000 to 43.5 in 2004 in primary care in Valencia, Spain (Ubeda et al., 2007).

Within antidepressants, the present study found a greater increase in the use of SSRI subclass (measured as the annual DDDs per 1000 registrants per day) compared to the remaining subclasses of antidepressants. This was followed by the other antidepressants subclass; however, only a minimal change in the use of the TCA subclass was measured. This finding was also in line with patterns reported in previous studies. Aarts et al. (2014) reported that the largest increase over time was seen in SSRI prevalence, with a 5.8-fold increase between 1991 and 2011, compared to a 2.1-fold increase in other antidepressant use, while the prevalent use of TCA remained relatively stable (Aarts et al., 2014). A similar finding was reported by Parabiaghi et al. (2011), who also found that SSRIs accounted for 44.8% of antidepressant use in Italy in 2000 and rose to 75.7% in 2007. This change reflects changes in the recommendations for depression treatment, with SSRIs recommended as first-line therapy (NICE, 2009).

The drop in TCA from 2013 onwards was mirrored by the increase in prescribing of the other antidepressants subclass over the same period. The increased use of the other antidepressants subclass within the population of patients with KOA could have been due to the research findings on the efficacy of duloxetine for OA-related pain (Chappell et al., 2011). Additionally, duloxetine was included as a therapeutic option in the OARSI guidelines for the non-surgical management of KOA, as a second- or third-line therapeutic option (McAlindon et al., 2014). It is well known that physicians' prescribing behaviours are influenced by various factors, including the results of major RCTs and guideline recommendations

(Bedson et al., 2013). It is therefore possible that the change in the prescribing of TCA and the other antidepressants subclass may be a result of such influences on prescribing, despite not being recommended by NICE guidance.

4.5.3.2 Anti-epileptic drugs (AEDs)

The present study found a marked increase in the prescribing prevalence of AEDs, which was in line with previous research findings, and reflects the general increase in gabapentinoid prescribing. In the UK, the rate of patients newly treated with gabapentin increased from 230 to 679 per 100,000 persons per year, and with pregabalin from 128 to 379 from 2007 to 2017, i.e. the rate has tripled (Montastruc et al., 2018). Similarly, a 55-fold rise in gabapentin among patients without a seizure disorder (from 0.2 to 11.1 per 1000 persons) was observed, compared to only a two-fold increase from 21.6 to 41.3 per 1000 persons for patients with epilepsy in Canada (Leong et al., 2016). Since the above studies studied the utilisation of gabapentinoids in the general population, it is likely that the patients with KOA represented a subset of the general population of gabapentinoid users.

Unlike the present study's findings on the progressive increase of AED incident users, a rather dramatic increase in the incidence of new AED users was observed from 2005 to 2006 in a population-based study in Italy, where the cumulative incidence increased from 9.4 (95%CI 8.9, 9.9) to 15.5 (95% CI 14.8, 16.1) from 2003 to 2006. However, this was followed by a sudden drop to 5.0 (95%CI 4.6, 5.4) in 2007. The fall in 2007 was attributed to the

introduction of a policy measure which restricted the reimbursement criteria of gabapentin and pregabalin in non-epilepsy disorders (Italiano et al., 2015).

4.5.3.3 Opioids

The present study found that the number of opioid prescriptions per 1000 registrants increased by almost 70%. This increase reflects the increase in the national utilisation of opioids in the UK generally, as reported in several other studies in the UK (Ruscitto et al., 2015, Zin et al., 2014, Foy et al., 2016) and Europe (Hamunen et al., 2009). Changes in strong opioid utilisation were reported in the UK using data from CPRD in a cross-sectional study, which reported a continuous rise in the annual prevalence of non-cancer pain patients using strong opioids from 1.8 per 1000 to 9.2 patients per 1000 CPRD registrants (Zin et al., 2014). Although consistent with the present study, the estimates were derived from a population of non-cancer pain patients, and not specifically from those with KOA diagnoses. The increasing prevalence of opioid prescribing for primary care patients was also documented in a recent cross-sectional study, where the proportion of patients prescribed weak opioids nearly doubled (from 6.5% to 12.4% over 7 years), while the proportion prescribed a stronger opioid increased six-fold (from 0.13% to 0.85%) (Foy et al., 2016).

It is worth mentioning that the rise in opioid prescribing found in the present study is particularly noticeable from 2005 onwards. This could be explained by the availability of several strong opioid formulations around that time. For

example, the buprenorphine 7-day patch became available in 2005, and the fentanyl 12mcg patch was also licensed in 2005. Additionally, the global recall of the COX-2 inhibitor rofecoxib resulted in a sharp reduction in the use of NSAIDs, following the release of safety advice from the MHRA. This resulted in an increase in opioid prescribing among primary care patients (Bedson et al., 2013)

In the present study, the number of new opioid users per 1000 registrants started to decrease more noticeably after 2008, until the end of the study. This trend coincided with the release of osteoarthritis guidelines by NICE in 2008 (NICE, 2008). The guidelines recommended the use of non-pharmacological management as a core component, and the use of topical NSAIDs as the first-line strategy prior to oral NSAIDs. Following the release of NICE guidelines on the care and management of osteoarthritis in adults (NICE, 2008), Bedson et al. (2013) found an increase in the prescribing of topical NSAIDs around and after this time. The number of people prescribed topical NSAIDs rose from 272 per 10,000 registrants in 2001 to 602 per 10,000 registrants in 2009 (Bedson et al., 2013).

The reduction in the number of new opioid users could also be attributed to the impact of co-proxamol withdrawal in 2008. A reduction in the number of new users was reported by Bedson et al. (2013), where the incident number of co-proxamol (a weak opioid in combination with paracetamol) prescriptions dropped dramatically from 75 to 2 prescriptions per 10,000 registrants from the second quarter of 2002 to the fourth quarter of 2005. This occurred around the time that the UK Medicines Regulatory Health

Authority (MHRA) issued safety advice on the withdrawal of co-proxamol in January 2005 (Bedson et al., 2013).

Consistent with findings from the present study, increased tramadol utilisation was reported by the NHS Business Services Authority, with the number of daily defined doses in England increasing from approximately 5.9 million in 2005 to 11.1 million in 2012. Subsequently, tramadol was classified as a Schedule 3 controlled drug based on advice from the UK's Advisory Council on the Misuse of Drugs (ACMD, 2013), due to concerns about safety and the potential risk of misuse. Thereafter, tramadol prescribing would follow stricter prescription requirements, with clear dosage and recommended maximum supply of 30 days. Eventually, the utilisation of tramadol showed decline in 2014 and 2015, as reported in a recent study using data from CPRD (Chen et al., 2018).

The increase in the proportion of patients with higher OMEQ bands is consistent with the shift towards prescribing stronger opioids, reported in previous studies within the UK. The national trend has been the increased use of stronger opioids, which was also found in the study by Ruscitto (2015). Ruscitto reported a decrease in weak opioid users, with a large increase in the proportion of strong opioid users in Scotland from 0.2% in 1995 to 3.6% in 2010. The rise was predominantly accounted for by the use of morphine, oxycodone, fentanyl and tramadol, suggesting a shift from prescribing weak opioids towards prescribing strong opioids. However, the study did not separate analgesic use for cancer or non-cancer indications, hence may not be directly relevant to the population of patients with KOA.

Similarly, Bedson, in 2013, reported the doubling of strong opioid prescriptions from 545 to 1035 users per 10,000 registered population (Bedson et al., 2013).

4.5.3.4 NSAIDs

Unlike other drugs, for NSAIDs, the number of prescriptions, patients and DDD per 1000 CPRD registrants dropped from 2004/2005 onwards. Such a drop was consistent with findings from the general population, using data from a regional UK database (Bedson et al., 2013). The study found that from 2001 to 2004, the annual prevalence of COX-2 inhibitors increased from 167 per 10,000 registrants to 378 per 10,000 registrants, but then fell to 65 per 10,000 registrants by 2009 (Bedson et al., 2013).

The decreasing prevalence and incidence of NSAID prescribing may indicate a better adherence to clinical guidelines, which recommend their use for the shortest possible period and at the lowest effective dose (NICE, 2014b).

NSAIDs were the most frequently prescribed class reported in population-based studies, and were reported to be used by 77.6% (n= 238 536) and 56.6% (n= 29,562) (Birtwhistle et al., 2015) and 30% (n=611) (Knoop et al., 2017) of the patients, while in the present study, opioids were the most frequently used class for 79% of the patients during follow-up. The high prevalence of opioid prescribing found in the present study may be of concern, as opioids are recommended as second- or third-line therapy, after paracetamol and topical/systemic NSAIDs (NICE, 2014). However, this

might be explained by the fact that this cohort was identified based on physician-recorded diagnosis of KOA, which possibly means a condition with longstanding, possibly severe pain (Jordan et al., 2016). Research has shown that the recording of a diagnosis of OA is associated with longstanding symptoms and severe pain, and it may take between six and seven years for this to be recorded in patients' records (Birtwhistle et al., 2015).

4.5.3.5 Paracetamol

Data on the utilisation of paracetamol is scant, and until recently population-based studies had not routinely included paracetamol. Paracetamol use was often incorporated within the use of other classes, such as NSAIDs, and classified as simple analgesics or with opioid prescriptions (Ndlovu et al., 2014), hence it was not possible to compare its prevalence of use over time across studies. Paracetamol prevalence was measured in a population-based study of patients with KOA during the year prior to TKR (Inacio et al., 2018). The study reported an increase in paracetamol prescribing from 52.1% in 2001 to 61.4% in 2012 (n=1,205 and 1,087). However, this change was not statistically significant (p=0.913) (Inacio et al., 2018).

The prevalence of paracetamol use in the general population was self-reported in a study including 40,000 respondents, and was 38.3% among those with no chronic pain conditions, and up to 64% among those with chronic pain conditions (Dale et al., 2015). Paracetamol was used by 70%

of the patients during follow-up, which is higher than that reported by Dale et al. This is possibly due to the definition of paracetamol use applied in their study (the use of paracetamol at least once in the previous month), and the embedded possibility of recall bias leading to underestimation.

4.5.4 Days' Supply

Among all drug classes, antidepressants were prescribed for the longest duration, followed by NSAIDs, with a gradually increasing trend over the study years. The prolonged days' supply of antidepressants, along with the reduction in the number of new antidepressant users, indicates that antidepressants are used for prevalent patients. The prolonged use of antidepressants was also reported in studies conducted in UK primary care settings, where the long-term prescribing of antidepressants was found to be the main reason behind the increase in antidepressant prescribing in UK (Moore et al., 2009).

AEDs and paracetamol had the lowest days' supply per year, while opioids showed a slow increase over the study years but were generally low (<80 days/year) compared to antidepressants.

4.5.5 Strengths and Limitations

This study has a number of strengths. Firstly, the length over which the observation was conducted. A period of 16 years allowed a wide observation window, where changes in prescribing for patients with KOA

could be tracked, which allowed valuable insights into prescribing in UK primary care. Secondly, unlike some previous drug utilisation studies (e.g. Wilson et al., 2014), the present study quantified the use of a range of drug classes which are recommended by clinical guidelines (including paracetamol), and/or are being used in clinical practice for KOA-related pain. However, there are some limitations which must be considered. Firstly, the analysis was made using prescriptions generated in primary care, and assumptions were made that the prescribed drugs were actually dispensed and taken by patients, which may have led to overestimating overall drug utilisation. Having said that, it must be remembered that prescribing data is one of the main data sources for drug utilisation and pharmacoepidemiology studies. Secondly, there is the potential for underestimation of NSAID and paracetamol utilisation, as these agents are frequently accessed through OTC purchases, hence are not completely recorded in CPRD. Finally, the study did not investigate factors associated with the described changes in prescribing across study drug classes. While acknowledging these limitations, the scope of the study was to seek crude estimates of prescribing, and describe changes over time. Additionally, the measures of OMEQ doses and days' supply might be biased, as these measures were performed on complete cases.

4.6 Conclusion

This study described changes in the prescribing of a range of analgesic drugs commonly prescribed for patients with KOA over a 16-year period. There was an overall increase in the number of prescriptions, the proportion of patients, and the mean DDDs of prescribed antidepressants, AEDs, opioids and paracetamol throughout the study. However, the annual proportion of new users of these drug classes decreased during the study years. By contrast, the prevalence of NSAID prescribing (annual number of prescriptions and proportions of patients, including proportions of new users) showed a decreasing trend from 2005 onwards. The growing overall prevalence of prescribing for most of the studied drug classes, particularly opioids, calls for further investigation into drug exposure levels for individual patients, and a detailed examination and characterisation of individual drug utilisation patterns in patients with KOA.

Chapter 5 Patterns of Drug Utilisation Among Primary Care Patients with Knee Osteoarthritis

5.1 Introduction

When examining drug utilisation, it is important to quantify the exposure at an individual patient level, and one way to do so is to measure persistence of use. However, this can be challenging due to the lack of consistency in the methodology used for measuring persistence. Several models/methods for measuring persistence with chronic therapies, such as statins (Helin-Salmivaara et al., 2009) and antihypertensives (Corrao et al., 2010), were identified in the literature (Table 5-1) (Caetano et al., 2006).

Table 5-1 Models of Measuring Persistence Identified in the Literature

Model, Variable Type	**Description of the Measure**	**Limitation**
Anniversary, Dichotomous	Filling a prescription with a certain number of days around the anniversary of the first prescription e.g. prescription refilled within 30 days of anniversary	No consideration given to prescriptions within a 1-year interval
Minimum refills, Dichotomous	Dispensation of a minimum number of prescriptions per year e.g. minimum of 2 refills per year	No consideration of the dates of prescriptions within a 1-year interval
Refill sequence, Continuous	Interval between date of first prescription and the point when an unacceptable gap occurs between refills e.g. until a 90-day gap between refills occurs	The rationale for selection of a permissible gap (PG) between refills is not always clear
Proportion of days covered (PDC), Dichotomous	Prescribing of sufficient medication to cover a specific proportion of days within a fixed interval e.g. 80% PDC during a year	Consideration is not given to the precise start and end dates of prescription
Hybrid	Combines more than one model E.g. a combination of PDC 80% and PG of 30 days between refills.	

It is generally known that treatments for long-term conditions require the appropriate dose for the appropriate length of time (Santoleri et al., 2013). However, with analgesics, such as opioids, the dose and duration of use have been associated with potential risks, including addiction, misuse and overdose (Gilson et al., 2004), (Gomes et al., 2011, Chou et al., 2015, Rose et al., 2018). Additionally, the daily analgesic doses may vary widely between patients and often over time. As a consequence, previous studies have used different terminologies and definitions to describe persistence, based on the number of prescriptions, duration of use, or duration and intensity of drug use within this interval (Boudreau et al., 2009, Skurtveit et al., 2011, Fredheim et al., 2010, Fredheim et al., 2013, Bedson et al., 2016, Mellbye et al., 2016, James et al., 2019, Lind et al., 2019, Mosher et al., 2016, Lai et al., 2016, Bushnell et al., 2016) (Table 5-2).

The main issue with many of the above definitions is that only one dimension of persistence was assessed, namely the dose or duration of use. Additionally, the rationale for developing and applying such definitions was not always clear. It is not known whether any consideration was given to patient characteristics or their need for analgesia. For example, how the DDD level of 400 was decided, or when the number of 10 prescriptions per year was selected as a cut-off point for a long-term definition (Table 5-2).

Table 5-2 Examples of Terminologies and Definitions of Analgesic Use Patterns

Author, Year	Drug Class	Terminology	Definition
Boudreau, 2009	Opioids	Long term	Treatment episodes of longer than 90 days with ≥10 prescriptions dispensed or 120 days' supply within a year
Skurtviet, 2011	Weak opioids	Persistence	Receipt of opioids each year from 2005 to 2008 and in 2008 received >365 DDDs of opioids.
Fredheim, 2010	Opioids	Not specified	Categorised individuals as probably receiving opioids for chronic non-cancer pain if they were dispensed >400 DDDs per year.
Bradley, 2011	Opioids	Chronic therapy	Continuous use for 90 days.
Fredheim, 2013	Strong opioids	Long term	Second opioid prescription dispensed within 70 days of the first prescription, and dispensation of ≥1 prescription during each 365 days for the subsequent 5 years.
Bedson, 2016	Opioids	Long-term use episodes	Issuing of ≥3 prescriptions within 90 days of the date of the new opioid prescription. An episode of long-term use ended with a gap of ≥6 months without a prescription.
Mellbye, 2016	Opioids	Persistence	Dispensation of ≥180 DDDs or 4500 mg OMEQ during a 365-day period.
Mosher, 2018	Opioids	Long-term therapy	Treatment episode of >90 days that began within the first 30 days following opioid initiation date.
James, 2019	Opioids	Chronic use	Regular prescriptions for at least 3 months.
Lind, 2019	NSAID	Long-term episodes	Use of NSAID for ≥2 weeks, for a given type (oral or topical) among residential aged care facilities in Australia.
Busnell, 2016	Antidepressants	Persistence	A total of ≥180 prescription days' supply, allowing a 30-day grace period.
Lai, 2016	AEDs	Persistence	The treatment duration from the index prescription date to the earliest date of: switching, augmentation, discontinuation (no dispensing for >90 days after end date of previous prescription), hospitalisation or disenrollment.

Recently, a methodological study defined persistent use (of opioids) using criteria corresponding to the clinical characteristics of patients. The criteria were based on the amount of opioid dispensed and the number of quarters out of the year in which opioid prescriptions were dispensed. A persistent

user was defined as a person who used more than 180 DDDs per year and had prescriptions dispensed in at least three out of the four quarters of the year (Svendson et al., 2012). This definition corresponded to typical patients using opioids most days of the week, but not around the clock (Svendsen et al., 2012). The model provided an optimal measure of persistence, as it included two dimensions of persistence attributes: the intensity measured as the number of DDDs, as well as the length in time measured as the distribution of prescriptions in the year's quarters.

Despite the comprehensiveness in defining persistence, Svendsen et al. (2012) measured persistence during a calendar year, and not in terms of patient years (time with respect to starting therapy). Their study may, therefore, have included patients at various time points after starting opioids, which may potentially over- or underestimate the prevalence of persistent use due to the inclusion of both new and prevalent users.

Persistence with non-opioid analgesic use, namely NSAIDs and paracetamol, has not been adequately studied. Additionally, persistence with antidepressants and AEDs in painful conditions is understudied, as most of the studies on their persistence were conducted in patients with diagnosed depression and epilepsy, respectively.

The present study sought to describe patterns of analgesic prescribing within one year of the first prescription of each class, and to determine the proportion of persistent users within each class. The period of one year after therapy initiation was recognised as a critical period, during which patients

may exhibit various drug use patterns, including switching, discontinuation, augmentation and termination of therapy (Gore et al., 2011).

The use of antidepressants and AEDs is assumed for the indication of pain management in patients with KOA, hence the study drug classes (antidepressants, AEDs, opioids, NSAIDs and paracetamol) are referred to as “analgesics” from this point onwards within this thesis.

5.2 Study Aim and Objectives

The overall aim of the present study was to describe patterns of analgesic use among primary care patients with KOA by determining the prescribed cumulative doses and the proportion of persistent users within one year of therapy initiation.

The specific objectives of the present study were to:

1. Describe the demographic characteristics of patients with KOA who used analgesics during follow-up.
2. Quantify the cumulative doses of each analgesic class prescribed for individual patients over the first year after initiation.
3. Determine the proportion of persistent users of each analgesic class.
4. Compare the demographic and clinical characteristics of persistent users and non-persistent users of the respective analgesic classes.

5.3 Methods

5.3.1 Study Design

This study was a retrospective cohort study of adults with KOA using CPRD data.

5.3.2 Study Population

From the overall study population of adult patients with KOA, which was identified in Chapter Three (n=117,637), this study included all patients who:

- Had their earliest record of KOA diagnosis between 1st January 2000 and 31st December 2015, preceded by no KOA diagnosis Read codes in their CPRD records (i.e. incident diagnosis of KOA). These patients would represent a subset of the overall selected population with KOA (the overall KOA population included incident as well as prevalent patients with KOA).
- Had at least one prescription of the study drugs during the follow-up period.

The selection of individuals with an incident diagnosis of KOA was to eliminate the potential biases introduced by the inclusion of prevalent cases, whose therapy patterns may have been influenced by factors such as duration since diagnosis.

Patients' age was recorded at the first prescription of each drug class, and was classified into four age ranks: <40, 40–64, 65–80 and >80 years. The classification of age into ranks was to measure the prevalence of drug class users per age rank. These age categories were chosen to characterise

distinct age bands related to KOA prevalence. Knee osteoarthritis usually starts after the age of 40 years, and its prevalence progressively increases with age until the age of 80 years, where a reduced pattern has been reported in previous epidemiological studies (Cisternas et al., 2016). Morbidities recorded prior to a year of KOA diagnosis date were captured. These included the chronic conditions that have been reported in patients with KOA in previous research (Alahumbra et al., 2014). The period of a year was chosen, as patients with chronic conditions are likely to have a primary care consultation within that time.

5.3.3 Observation Period

The index date which marked the entry into the cohort was defined as the date of the first prescription after the incident KOA diagnosis date, or the date of first prescription in a treatment episode inclusive of KOA diagnosis date. Patients with an incident diagnosis of KOA were followed up until the earliest date of the following: the end of the study period, transfer-out date, or death date.

5.3.4 Analgesic Prescriptions

Prescriptions of each analgesic class (antidepressants, AEDs, opioids, NSAIDs and paracetamol) were selected from the patients' therapy files. Prescription data contained information on prescribing date, quantity, strength and daily dose. The duration of each prescription was calculated

by dividing the quantity prescribed by the numeric daily dose (NDD). Within antidepressants, the SNRIs were presented separately from the other antidepressant subgroup and included duloxetine and venlafaxine. This was to characterise exposure to this group (i.e. SNRIs) in more detail. The classification of AEDs into older and newer, opioids into weaker and stronger, and NSAIDs into non-selective and COX-2 inhibitors was consistent with the classification applied previously (see Chapter 4).

Within general practice, in many instances, prescriptions for a particular patient are generated at fairly regular intervals of up to approximately two months' duration. This reflects a pattern of prescribing when a patient requires a repeat prescription at regular intervals because they have used up their previous supply of medication. Sometimes, the interval between prescriptions is much longer, during which it is assumed that the patient was not taking any medicine. The time elapsed between prescriptions was analysed and it was found that most prescriptions were generated for individual patients at intervals of up to 60 days.

Accordingly, treatment episodes were defined as a period of respective analgesic use without gaps of more than 60 days between the end of a prescription and the start of the next prescription. A prescription after more than 60 days was counted as the start of a new episode. Treatment episodes were constructed to mark the index date of the first prescription in a treatment episode, inclusive of the diagnosis of KOA. Prescriptions generated within one year of initiation of each analgesic class were included in the analysis (Figure 5-1).

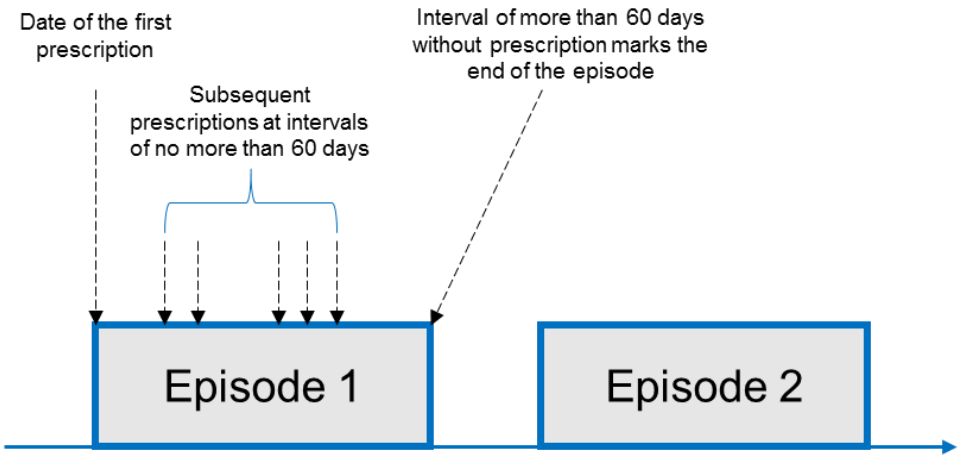


Figure 5-1 Illustration of How Prescriptions Generated at Intervals of no more than 60 Days are Treated as Discrete Episodes of Exposure.

5.3.5 Study Outcomes

The following outcomes were measured within the present study:

1. Demographic characteristics of patients with KOA stratified according to analgesic class during follow-up.
2. The proportion of patients with an incident diagnosis of KOA and their prescription data (total number of prescriptions within follow-up and within the first year of treatment). Comorbidities recorded in the year before the index diagnosis date including: depression, seizure disorders, coronary heart disease (CHD), diabetes, hypertension, stroke and chronic obstructive pulmonary disease (COPD). These were identified using appropriate Read codes in the patient records (clinical, consultation and referral files using code lists available from the Quality and Outcome Framework (QOF) business rules as well as

codes from Cambridge 2018 version1). Lists of the Read codes used are included in (Appendix 1 Table 1.4).

3. Cumulative doses of respective analgesics were calculated. The quantity of each prescription was multiplied by the strength (in milligrams) of the prescription to calculate the amount of each prescription. The result was then divided by the DDD of that particular drug or formulation to generate the dose in DDD per prescription. For transdermal formulations of opioids (fentanyl and buprenorphine), the strength per hour and the duration of delivery were considered in the dose calculation. The cumulative dose received by each patient within the first year following therapy initiation was the sum of doses of each prescription during that period.

   The cumulative doses per year were classified into four categories: low, intermediate, high and very high cumulative analgesic doses. The low dose was defined as a total use of <30 DDDs per year, while the intermediate, high and very high cumulative doses were those with totals of 30–90, 90–180 and >180 DDDs, respectively. These categories were selected to reflect less than a month's use of analgesics, up to 3 months' use, up to 6 months' use, and more than 6 months' use over one year following initiation.

4. The proportion of patients who were persistent analgesic users during the first year following therapy initiation. The definition of persistent analgesic use was adopted from work on opioids by researchers from Norway (Svendson et al., 2012). In the present study, a persistent user

of an analgesic was defined as a patient who used a cumulative dose of more than 180 DDDs per year and had prescriptions issued during three out of the four quarters of the year. The demographic and prescription data of persistent and non-persistent users were compared.

The definition of persistence was selected as it addressed analgesic use from more than one dimension, i.e. included the amount of analgesic use over a year and the distribution of prescriptions throughout the year, which reflects a pattern of continuous or prolonged use. Clinically, the definition is meaningful, as it indicates the use of opioids for at least six months in a year, and is comparable to receiving an average of approximately 15mg/day of oral morphine or 60 mg/day of codeine (Mellbye et al., 2016).

5.3.6 Data Analysis

Descriptive statistics (frequencies and percentages) were used to describe the study cohort according to analgesic classes and subclasses. The cumulative dose during the first year after prescribing was calculated for each patient, and the proportion of persistent users was determined. Comparisons between persistent and non-persistent users for demographic and prescription data were conducted,

5.3.7 Data Management

All extracted variable data was checked for any missing data. It was found that variable proportions of the prescription records were missing for numeric daily dose (NDD) data (Table 5-3). Numeric daily dose information was required to calculate prescription duration and to construct treatment episodes, which were then used to select prescriptions for inclusion in the analysis. Between 0.02% and 0.03% of the total prescriptions had the prescribed quantity missing which could not be derived, and hence were dropped (n=51 prescriptions of antidepressants, 43 of AEDs, 154 of opioids, 23 of NSAIDs, and none of paracetamol).

Table 5-3 Number and Percentage of Prescriptions with Missing NDD

Analgesic Class	Total Included Prescriptions	Prescriptions with Missing NDD (%)
Antidepressants	1,691,917	261,652 (15.4)
AEDs	521,403	141,665 (27.2)
Opioids	2,642,601	754,135 (28.5)
NSAIDs	805,319	109,419 (13.6)
Paracetamol	1,552,036	342,265 (22.0)

NDD: numeric daily dose; AED: antiepileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs

The missing NDD information was managed following a sequential order so as to make the best use of available recorded data within CPRD, and to provide the most explicit and accurate daily dose information. The present method was applied within drug utilisation studies using CPRD data (Baker, 2017). For antidepressants, AEDs, NSAIDs and paracetamol, missing NDD information was managed using patients' own dosing information, where the median NDD of the same product was used to impute the missing NDD. When the NDD was missing throughout a patient's record, the median NDD

of the population for the same product was used. Any remaining missing NDDs were imputed using information from the common dosage CPRD look-up file (Figure 5-2).

For opioids, in the first stage, prescriptions with missing NDD for strong opioids that are recommended for use at defined single time-intervals were imputed based on the daily dose information provided by the BNF (BNF, 2014). For example, for a fentanyl 25mcg/hour patch, the BNF recommendation is 1 patch to be used every 72 hours; therefore, the daily numerical dose or NDD for a fentanyl 25mcg patch would be 0.33, and this was imputed as such. The remaining missing NDD information was imputed by applying strategies used with other study analgesic classes, as detailed above and summarised in Figure 5-2.

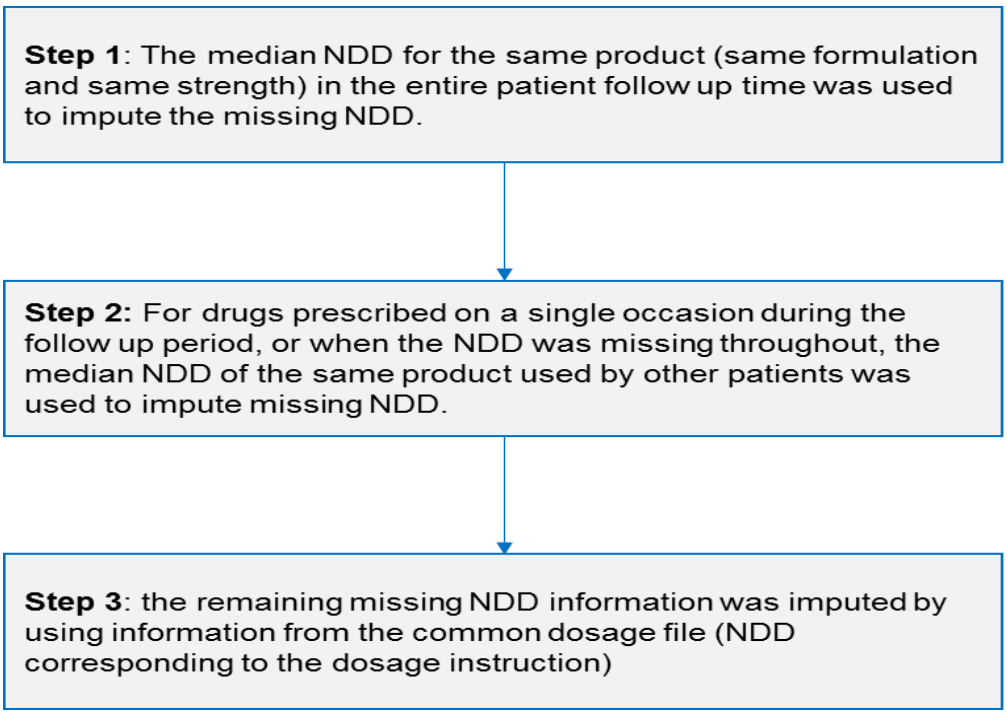


Figure 5-2 Strategies for Imputing Missing NDD.

5.3.8 Imputation Results and Diagnostics

Results on the number of prescriptions imputed and remaining after the application of the imputation strategy are shown in Table 5-4. For opioids, the step of using BNF dosing information for the imputation of strong opioid patch formulation, as described above, was mentioned as “step 0” within Table 5-4. Imputation diagnostics were performed, and the results showed only a slight increase in the mean and median NDD values after imputation (Table 5-5). This demonstrates the reliability and appropriateness of the strategies followed for imputation.

Table 5-4 Number of Prescriptions Imputed and Remaining after Each Step

Analgesic Class	Number of Prescriptions with Missing NDD	Number Imputed	Remaining Prescriptions with Missing NDD
Antidepressants			
Step 1	261,652	149,964	111, 688
Step 2	111, 688	111, 287	401
Step 3	401	401	0
AEDs			
Step 1	141,665	65,466	76,199
Step 2	76,199	75,842	357
Step 3	357	357	0
NSAIDs			
Step 1	109,419	61,503	47,916
Step 2	47,916	47,828	88
Step 3	88	88	0
Paracetamol			
Step 1	342,265	170,513	171,752
Step 2	171,752	17,138	414
Step 3	414	414	0
Opioids			
Step 0*	754,135	63,792	690,343
Step 1	690,343	252,199	438,144
Step 2	438,144	403,298	34,846
Step 3	34,846	34,846	0

NDD: numeric daily dose * used BNF dosing for imputation of strong opioid patch formulations

Table 5-5 Mean (SD) and Median (IQR) Used to Compare the Distribution of NDD Before and After Imputation

	Mean NDD (SD)		Median NDD (IQR)	
	Before imputation	**After imputation**	**Before imputation**	**After imputation**
Antidepressants	1.20(2.10)	1.33(2.05)	1(1,1)	1(1,1.5)
AEDs	2.45(1.02)	2.65(1.75)	2(0,3)	2(2,3)
Opioids	4.4(2.8)	5.2(2.1)	6(0,6)	6(1,9)
NSAIDs	1.96(6.90)	2.16(7.18)	2(1,3)	2(1,3)
Paracetamol	5.36(3.78)	6.12(3.41)	6(5,8)	6(6,8)

AED: antiepileptic drugs; NDD: numeric daily dose; SD: standard deviation; IQR: inter quartile range

5.4 Results

5.4.1 Demographic Characteristics of Analgesic Users

Overall, 117,637 patients with KOA were selected from CPRD and constituted the study population, as described above in section 5.3.2. Their demographic characteristics are presented in Table 5- 6, stratified according to the prescribed analgesic class.

Most patients in the selected cohort (79.1%) were prescribed opioids at some point in time during follow-up (93,007/117,637), while a smaller proportion (n=82,497; 70.0%) were prescribed paracetamol. Patients with KOA were prescribed NSAIDs at a mean age of 62.58 (SD 12.8) years, while the mean ages at which AEDs and paracetamol were initiated were 66.95 years (SD 12.9) and 66.98 (SD 12.4) years, respectively (Table 5-6).

Table 5-6 Demographic Characteristics of the Study Cohort

Analgesic Class	Antidepressants	AEDs	Opioids	NSAIDs	Paracetamol
No. patients	n=53,467	n=15,814	n=93,007	n=84,750	n=82,497
Gender (% of total prescribed respective class)					
Males	16,978 (31.7)	5,441 (34.4)	36,407 (39.1)	34,314 (40.5)	30,634 (37.2)
Female	36,489 (68.3)	10,373 (65.6)	56,600 (60.9)	50,436 (59.5)	51,863 (62.8)
Age at therapy initiation (years)					
Mean (SD)	64.46 (13.90)	66.95 (12.96)	64.69 (12.83)	62.58 (12.83)	66.98(12.40)
Age ranks (years) of all patients with KOA (% of total prescribed respective class)					
<40	2,150 (4.0)	337 (2.1)	2,906 (3.1)	3,492 (4.1)	1,813 (2.2)
40–64	25,127 (47.0)	6,420 (40.6)	43,478 (46.8)	44,688 (52.7)	32,842 (39.8)
65–80	18,278 (34.2)	6,409 (40.5)	35,447 (38.1)	28,982 (34.2)	35,421 (42.9)
>80	7,912 (14.8)	2,648 (16.8)	11,176 (2.0)	7,588 (9.0)	12,421 (15.6)
Males with KOA (% of total males prescribed respective drug class)					
<40	642 (3.8)	106 (1.9)	1,156 (3.2)	1,491 (4.4)	615 (2.0)
40–64	8,513 (50.1)	2,305 (42.4)	18,264 (50.2)	19,547 (56.9)	12,904 (42.1)
65–80	5,693 (33.5)	2,265 (41.6)	13,626 (37.4)	11,108 (32.4)	13,318 (43.5)
>80	2,130 (12.5)	765 (14.1)	3,361 (9.2)	2,168 (6.3)	3,797 (12.4)
Total (100%)	16,978	5,441	36,407	34,314	30,634
Females (% of total females prescribed respective drug class)					
<40	1,508 (4.1)	231 (2.2)	1,750 (3.1)	2001 (3.9)	1,198 (2.4)
40–64	16,614 (45.5)	4,115 (39.7)	25,214 (44.5)	25,141 (49.9)	19,938 (38.4)
65–80	12,585 (34.5)	4,144 (39.9)	21,821 (38.6)	17,874 (35.4)	22,103 (42.6)
>80	5,782 (15.9)	1,883 (18.2)	7,815 (13.8)	5,420 (10.8)	8,624 (16.6)
Total (100%)	36,489	10,373	56,600	50,436	51,863

AED: antiepileptic drugs; NSAID: Non-steroidal anti-inflammatory drugs; SD: standard deviation

Of the four age ranks, there were higher proportions of patients aged 40 to 64 years among antidepressant, opioid and NSAID users (representing

47%, 46.8% and 52.7% of total prescribed corresponding class, respectively), while a higher proportion of patients within the older age group (65–80 years) were paracetamol users, representing 42.9% of all paracetamol users. Those using AEDs were equally distributed between the 40–64 and 65–80 years age ranks (n=6,420 and 6,409 patients), representing 40.6% and 40.5% of total AED users. Females constituted the majority of users across all five drug classes, representing 59.5% of total NSAID users (50,436/84,750) and 68.3% of total antidepressant users (36,489/53,467). The number of patients with KOA, stratified by gender and analgesic class, is summarised in Figure 5-3.

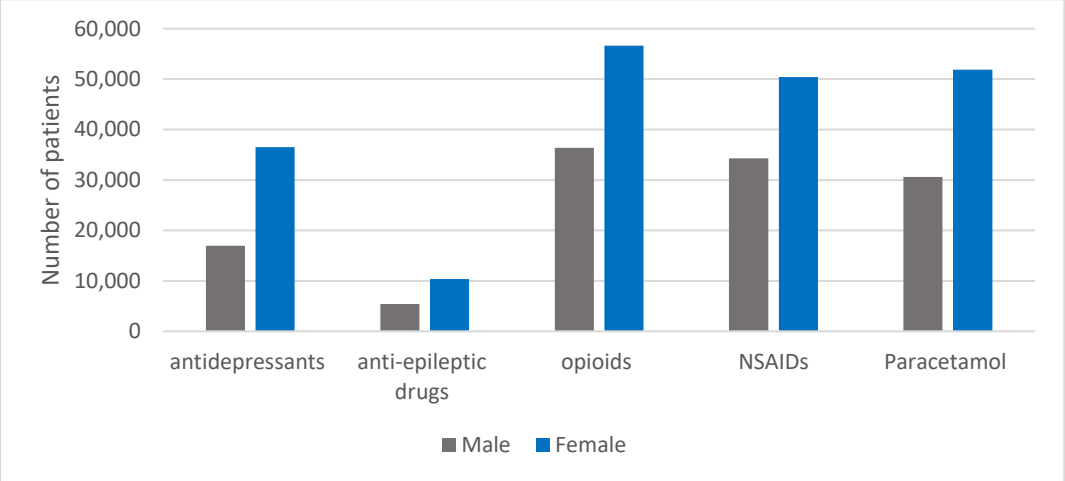


Figure 5-3 Patients with KOA by Analgesic Class and Gender.

5.4.2 Selection of Patients with an Incident Diagnosis KOA

Out of the 117,637 patients who constituted the overall study population, the present study included 108,221 patients (91.9%) who had their earliest

recorded diagnosis (incident diagnosis) of KOA between 2000 and 2015, preceded by no such record in their data. Those patients represented a subset of the overall selected population of KOA (117,637), which included patients with any KOA diagnosis record (incident or prevalent). The characteristics of the present study's cohort are shown in Table 5- 7.

The distribution of patients within age ranks differed according to the prescribed analgesic class. Most of those who were prescribed AEDs, opioids, or paracetamol were aged between 65 and 80 years (43.2%, 43.8% and 48% of total in the respective classes n=5,735, 33,257 and 31,385). Most of those prescribed antidepressants and NSAIDs were between 40 and 64 years (n=16,446 and 23,933 representing 41.2% and 44.5%, respectively). More than 20% of the patients who were prescribed antidepressants or AEDs had at least one comorbid condition (21.2% and 24.1% of total users of the respective classes). There were 3,650 patients (6.8% of all NSAID users) who also had a cardiovascular condition recorded within one year prior to the date of incident KOA diagnosis (Table 5-7).

Table 5-7 Characteristics of Patients with an Incident KOA Diagnosis

	Antidepressants	AEDs	Opioids	NSAIDs	Paracetamol
Total No. patients	53,467	15,814	93,007	84,750	82,497
No. of patients with an incident diagnosis of KOA (% of total)	39,906 (74.6)	13,257 (83.8)	75,977 (81.7)	53,809 (63.5)	65,350 (79.2)
Gender (% of patients prescribed respective class)					
Males	12,322 (30.9)	4,560 (34.4)	29,282 (38.5)	21,563 (40.1)	23,842 (36.5)
Female	27,584 (69.1)	8697 (65.6)	46,695 (61.5)	32,246 (59.9)	41,508 (63.5)
Age at therapy initiation (% of patients prescribed respective analgesic class)					
Mean (±SD)	66.4 (13.40)	66.5 (13.76)	67.5 (12.43)	65.2 (12.27)	70.20 (11.87)
Age ranks in years (% of patients with an incident KOA diagnosis prescribed respective analgesic class)					
<40	928 (2.3)	273 (1.8)	1,125 (1.5)	1,094 (2.0)	574 (0.9)
40–64	16,446 (41.2)	4,871 (36.7)	28,554 (37.6)	23,933 (44.5)	18,955 (29.0)
65-80	15,391 (38.6)	5,735 (43.2)	33,257 (43.8)	22,293 (41.4)	31,385 (48.0)
>80	7,141 (17.9)	2,414 (18.3)	13,041 (17.1)	6,489 (12.1)	14,436 (22.1)
Comorbid conditions (% of patients prescribed respective analgesic class)					
1 comorbidity	7,469 (18.7)	2,813 (21.2)	8,492 (9.1)	7,237 (13.4)	5,215(6.3)
≥2 comorbidities	1,012 (2.5)	390 (2.9)	2,355 (2.5)	772 (1.4)	2,344 (2.8)
Depression	3,790 (9.5)	939 (3.0)	3,542 (4.7)	2,413 (4.5)	2,922 (4.5)
Epilepsy	334 (0.8)	781 (5.9)	595 (0.8)	362 (0.7)	556 (0.9)
Diabetes	1,458 (3.7)	555 (4.2)	2,617 (3.4)	1,600 (3.0)	2,385 (3.6)
Cardiovascular diseases	2,991 (7.5)	991 (7.5)	5,731 (7.5)	3,650 (6.8)	5,411 (8.3)
Stroke	296 (0.7)	110 (0.8)	491 (0.6)	242 (0.4)	512 (0.8)
COPD	711(1.8)	260 (2.0)	1,187 (1.6)	569 (1.1)	1,053 (1.6)

AEDs: antiepileptic drugs; SD: standard deviation; IQR: interquartile range; COPD: chronic obstructive airway disease

5.4.3 Analgesic Prescription Data

A total of 7,213,276 prescriptions were generated for the 108,221 primary care patients with an incident diagnosis of KOA, and were included in the analysis. Approximately half (50.6%) of them were generated after the date

of incident KOA diagnosis, while 49.4% constituted an episode inclusive of the diagnosis date (n=3,653,232 and 3,560,044, respectively). The figures regarding included patients and prescriptions stratified by drug classes and subclasses are shown in Table 5-8.

Table 5-8 Number (%) prescriptions during follow-up and during the first year after initiation, stratified by analgesic class

	No. Patients* N= 108,221	**No. Prescriptions In Follow-up, n (%)**	**No. Prescriptions In the First Year, n (%)**
Antidepressant			
Total	39,906	1,691,917	292,787
TCA	25,920	689,047 (40.7)	119,104 (40.7)
SSRIs	21,515	745,891 (44.1)	141,193 (48.2)
MAOI	48	2,177 (0.1)	282 (0.1)
SNRIs	3,812	137,355 (8.1)	15,142 (5.2)
Other antidepressants	4,962	117,447 (7.0)	17,066 (5.8)
AEDs			
Total	13,257	521,403	101,890
Old AEDs	2,949	264,022 (50.6)	28,496 (28.0)
New AEDs	10,787	257,381 (49.4)	73,394 (72.0)
Opioids			
Total	75,977	2,642,601	462,124
Weak	68,937	1,827,802 (69.2)	359,582 (77.8)
Strong	19,349	814,799 (30.8)	102,542 (22.2)
NSAIDs			
Total	53,809	805,319	218,229
Non-selective	50,509	666,926 (82.8)	182,568 (83.7)
COX-2	11,240	138,393 (17.2)	35,661 (16.3)
Paracetamol			
	65,350	1,552,036	329,515

*Patients with a new diagnosis of KOA between 1st Jan 2000 and 31st January 2015. Some patients used combinations.

Most antidepressant users were prescribed TCAs (64.9%) or SSRIs (53.9%) (n=25,950 and 21,515, respectively). Among the AED users, users of newer AEDs were predominant, representing 81.4% of the total, compared to 22.2% of patients prescribed older AEDs (n=10,787 and 2,949,

respectively). Users of weak opioids constituted the majority of those who were prescribed opioids, with weak opioids prescribed for 90.7% (n=68,937) during follow-up, while non-selective NSAID users were predominant among those prescribed NSAIDs, with non-selective NSAIDs prescribed for 93.4% of total NSAID users (n=50,509).

Prescription data, including details of the number of prescriptions during follow-up and during the first year after initiation of the respective analgesic class, as well as the duration of analgesic prescriptions in follow-up, is presented in Table 5-9.

A quarter (24.9%) of NSAID users (n=13,388) had only a single prescription during follow-up, which represented the largest proportion of single-prescription users compared to the other classes. Within the opioids class, single-prescription patients represented 15.2% (n=11,589), which was the lowest compared to 17.6% of antidepressant users, 21.1% of AED users and 18.8% of paracetamol users (n= 7,082, 2,805 and 12,350 patients, respectively) (Table 5-9).

Antiepileptic drug users received a median of 131 (IQR 58,309) prescriptions during follow-up, which was the highest across studied analgesic classes, followed by opioid users, who received a median of 111 (IQR 51,210) prescriptions. The median numbers of total prescriptions for antidepressants, NSAIDs and paracetamol were 14 (IQR 2, 53), 48 (IQR 20, 89) and 62 (IQR 31, 110), respectively (Table 5-9).

Table 5-9 Total Number (%) of prescriptions per patient

	Antidepressants N=39,906	**AEDs N=13,257**	**Opioids N=75,977**	**NSAIDs N=53,809**	**Paracetamol N=65,350**
Total no. respective analgesic prescriptions per patient during follow-up, n (%)					
1	7,028 (17.6)	2,805 (21.2)	11,589 (15.2)	13,388 (24.9)	12,281 (18.8)
2–6	8,466 (21.2)	3,257 (24.5)	22,268 (29.3)	18,734 (34.8)	17,367 (26.6)
7–12	3,781 (9.5)	1,268 (9.6)	9,071 (11.9)	6,405 (11.9)	7,890 (12.1)
13–24	4,418 (11.1)	1,490 (11.2)	8,699 (11.4)	5,732 (10.6)	8,636 (13.2)
25–36	3,132 (7.8)	954 (7.2)	5,123 (6.7)	3,048 (5.7)	5,516 (8.4)
37–48	2,308 (5.8)	690 (5.2)	3,501 (4.6)	1,894 (3.5)	3,571 (5.5)
49–60	1,796 (4.5)	471 (3.5)	2,648 (3.4)	1,346 (2.5)	2,613 (4.0)
>60	8,977 (22.5)	2,322 (17.5)	13,078 (17.2)	3,262 (6.1)	7,476 (11.4)
Total number of prescriptions per patient during follow-up					
Median (IQR)	14 (2,53)	131 (58,309)	111 (51,210)	48 (20,89)	62 (31,110)
Total analgesic prescriptions per patient in first year after prescribing, n (%)					
1	9,930 (25.0)	3,403 (25.7)	21,277 (28.0)	20,150 (37.4)	20,834 (31.9)
2–3	5,754 (14.4)	2,181 (16.5)	17,730 (23.4)	13,118 (24.4)	13,990 (21.4)
4–6	5,278 (13.2)	1,628 (12.3)	11,769 (15.5)	8,351 (15.5)	10,778 (16.5)
7–12	11,059 (27.7)	3,212 (24.2)	14,345 (18.9)	9,546 (17.7)	14,095 (21.5)
≥ 13	7,885 (19.7)	2,833 (21.3)	10,856 (14.2)	2,644 (4.9)	5,653 (8.7)
Total number of prescriptions per patient in first year					
Median (IQR)	12 (8,15)	13 (8,18)	43 (14, 104)	8 (4,11)	12 (8,15)

AEDs: antiepileptic drugs; NSAID: non-steroidal anti-inflammatory drugs; IQR: interquartile range

The total duration of analgesic use by individual patients ranged from 1 day to more than 5 years (Table 5-10), with antidepressants used for the longest

duration during follow-up (median duration 504 [IQR 84,1888]). The median total durations of antidepressants and AEDs prescriptions within the first year were 200 (IQR 56,360) days and 180 (IQR 120,365) days – greater periods than for the other classes, for which the median total durations were 56 (28,180), 50 (16.7, 150) and 50 (16,130) days for NSAIDs, opioids and paracetamol, respectively (Table 5-10).

Table 5-10 Total Duration of Prescriptions in Follow-up

	Antidepressants N=39,906	**AEDs N=13,257**	**Opioids N=75,977**	**NSAIDs N=53,809**	**Paracetamol N=65,350**
1–28 days	4,665 (11.6)	1,415 (10.7)	15,562 (20.5)	12,506 (23.2)	14,389 (22.0)
29–84 days	5,785 (14.5)	3008 (22.7)	15,456 (20.3)	12,221 (22.7)	12,817 (19.6)
85–180 days	3,882 (9.7)	1,543 (11.6)	9,949 (13.1)	7,778 (14.5)	8,000 (12.2)
181–365 days	3,892 (9.8)	1,389 (10.5)	8,313 (10.9)	5,996 (11.1)	8,537 (13.1)
1–<2 years	4,305 (10.8)	1,495 (11.3)	7,926 (10.5)	5,340 (9.9)	8,668 (13.2)
2–<3 years	2,990 (7.6)	907 (6.8)	4,549 (6.0)	2,885 (5.4)	4,759 (7.3)
3–<4 years	2,304 (5.8)	617 (4.6)	2,894 (3.8)	1,854 (3.4)	2,824 (4.3)
4–5 years	1,810 (4.5)	473 (3.6)	2,257 (3.0)	1,286 (2.3)	1,814 (2.8)
>5 years	10,273 (25.7)	2,410 (18.2)	9,071 (11.9)	3,943 (7.3)	3,542 (5.4)
Total duration of prescriptions in follow-up					
Median (IQR) in days	504 (84, 1888)	392 (289,504)	142.5 (33,716)	112 (30,462)	144 (33 ,554)
Total duration of prescriptions in one year after initiation					
Median (IQR) in days	200 (56,360)	189 (42, 365)	50 (16.7, 150)	56 (28,180)	50 (16,130)

AEDs: antiepileptic drugs; NSAID: non-steroidal anti-inflammatory drugs; IQR: interquartile range

5.4.4 Cumulative Doses

The cumulative annual exposure (DDD per patient per year) for each analgesic class is shown in Tables 5-11 to 5-15.

5.4.4.1 Cumulative Doses of Antidepressants

Within the first year following treatment initiation, a total of 13,187 (33%) antidepressant users used cumulative doses of less than 30 DDDs per year, while 14,713 (36.9%) used >180 DDDs per year. The majority (79.9%) of low-dose users were prescribed tricyclic antidepressants (10,546/13,186), while the majority (57.7%) of high-dose users were prescribed SSRIs within one year of initiation of antidepressant therapy (8,494/14,713) (Table 5-11). Users of MAO inhibitors within the first year after their initial prescription (n=13) were not included in further analyses, because cells were of values less than 5.

Table 5-11 Antidepressant Users Stratified by Cumulative Dose

	Total	**TCA**	**SSRIs**	**SNRIs**	**Other**	**Combined**
N (row %)	n=39,893	18,910 (47.4)	14,020 (35.1)	914 (2.3)	1131 (2.9)	4,918 (12.3)
Cumulative dose DDD/patient/year (column %)						
<30	13,186 (33.0)	10,546 (55.7)	1,969 (14.0)	154 (16.8)	341 (30.1)	176 (3.6)
30–90	7,045 (17.7)	3,894 (20.6)	1,980 (14.1)	98 (10.7)	165 (14.6)	904 (18.4)
91–180	4,961 (12.4)	2,382 (12.6)	1,577 (11.2)	92 (10.1)	144 (12.7)	766 (15.6)
>180	14,713 (36.9)	2,088 (11.0)	8,494 (60.6)	570 (62.4)	481 (42.5)	3,072 (62.5)

DDD defined daily doses TCA tricyclic antidepressants SSRIs selective serotonin reuptake inhibitors SNRI Serotonin Norepinephrine Reuptake Inhibitors other: other antidepressant sub-class combined: prescribed more than one subclass during the first year after therapy initiation.

Those who have used more than one subclass of antidepressants within one year following initiation (referred to with the combined column heading in Table 5-11) had a higher proportion of high-dose users, with 62.5% (n=3,072) of them prescribed >180 DDDs per year, compared to 11.0% (n=2,088) of tricyclic antidepressant users, 60.6% (n=8,494) of SSRI users, 62.4 % (n=570) and 42.5% (n=418) of SNRI and other antidepressant users.

5.4.4.2 Cumulative Doses of AEDs

The cumulative doses of 39% (n=5,177) of AED users were less than 30 DDDs per year; however, nearly a quarter (23.8%) of them (n=3,166) were prescribed >180 DDDs within one year of their first prescription. Higher cumulative doses were more prevalent among those who only used older AEDs, with 35% using >180 DDDs within one year of prescribing, while the lower cumulative doses were more prevalent in those who were prescribed only newer AEDs, with 42.8% using less than 30 DDDs per year. Among those who used both older and newer AEDs, the proportion of patients using higher cumulative doses was prominent (46.5%) (Appendix 6).

5.4.4.3 Cumulative Doses of Opioids

Three quarters (74.5%) of opioid users were prescribed weak opioids, and less than 10% were prescribed only strong opioids; however, 16.2% of the patients were prescribed both weak and strong opioids within one year of

their first prescription (n= 56,757, 7,060 and 12,338, respectively) as presented in Appendix 6.

Opioids were prescribed mostly in low doses during the first year, with 45.9% of the patients prescribed less than 30 DDDs per year (n=34,880). Nonetheless, there were 11,345 patients who were prescribed >180 DDDs per year (15%). The use of higher cumulative doses per year was more prevalent among patients who used both weak and strong opioids within one year of their first prescription, with 31.3% of them using >180 DDDs per year (3,844/12,309).

5.4.4.4 Cumulative Doses of NSAIDs

Out of the 53,908 patients who used NSAIDs during follow-up, 42,658 (79.1%) were prescribed only non-selective agents, while 3,306 (6.2%) used only COX-2 inhibitors, and 7,944 (14.7%) used both non-selective agents as well as COX-2 inhibitors during the first year after NSAID therapy initiation. The cumulative doses of NSAIDs over the first year following therapy initiation are presented in Appendix 6.

5.4.4.5 Cumulative Doses of Paracetamol

For paracetamol users, 32.7% and 30.1% (n= 21,366 and 19,755, respectively) used up to 90 DDD per year, while 19.7% (n=12,907) used up to 180 DDDs, and 17.5% (n= 11,453) used more than 180 DDDs during the

first year after their first prescription (Appendix 6). This pattern of use indicates that more than 60% of those who were prescribed paracetamol used it for up to 3 months, nearly 20% of them used paracetamol for up to 6 months, and 17.5% used it for more than 6 months during the first year after their first prescription. A graphical summary of cumulative doses within each analgesic class is shown in Figure 5-4.

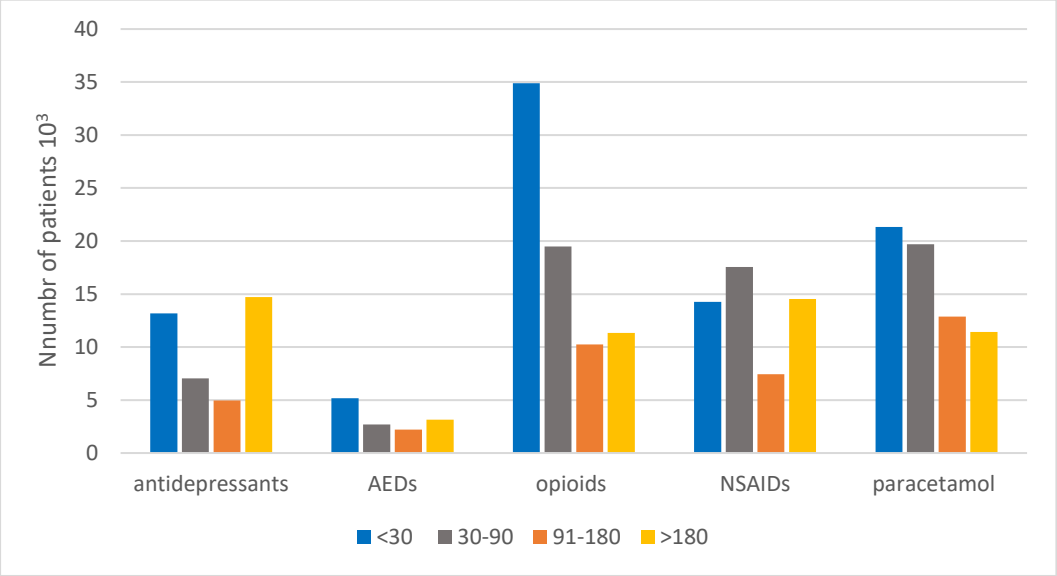


Figure 5-4 Number of Patients by Cumulative Doses of Analgesic Classes (in DDDs) Within the First Year of Treatment.

5.4.5 Persistent Use of Analgesics

5.4.5.1 Proportion of Persistent Users

By the end of the first year after prescription of the respective analgesics, the proportions of patients who were persistent users of analgesics ranged

from 14.9% (of opioids) to 36.8% (of antidepressants) (n=11,345 and 14,708, respectively). The proportions of persistent users of analgesics within one year following their first prescription are presented in Table 5-12.

Table 5-12 Numbers (%) of Persistent Analgesic Users

Number of Patients	Antidepre-sants	AEDs	Opioids	NSAIDs	Paraceta-mol
Total	39,906	13,257	75,977	53,809	65,350
Prescriptions Distributed in three Quarters / Year	26,428 (66.2)	8,484 (63.9)	24,789 (32.6)	25,285 (46.9)	35,998 (55.0)
Patients who used >180 DDD / Year	14,713 (36.9)	3,166 (23.8)	11,345 (14.9)	14,542 (27.0)	11,431 (17.5)
Number of Persistent users	14,708 (36.8)	3,157 (23.8)	11,345 (14.9)	14,542 (27.0)	11,431 (17.5)

DDD defined daily doses AED Anti-epileptic drugs NSAIDs non-steroidal anti-inflammatory drugs.

Across analgesic classes, the proportion of patients who had prescriptions distributed throughout the year (at least one prescription in three out of four quarters of the year) was higher than the proportion using higher doses (i.e. >180 DDDs per year). For example, 63.9% of AED users had prescriptions distributed through three quarters of the year, while only 23.8% of them were prescribed >180 DDDs within one year after the initial prescription (n=8,484 and 3,166, respectively) (Table 5-12).

Among all five analgesic classes, the largest proportion of persistent users was antidepressant users, where 36.8% of the users had used antidepressants persistently (14,708/39,906). Nearly a quarter of AED and NSAID users had used their analgesics persistently within one year after their first prescription (representing 23.8% and 27.0%, n= 3,157 and 14,542 patients), while smaller proportions of opioid and paracetamol users (14.9%

and 17.5%, n= 11,384 and 11,453 patients, respectively) had persistently used their prescribed analgesics within the first year.

5.4.5.2 Characteristics of Persistent and Non-persistent Users

In the following subsections, the characteristics of persistent and non-persistent users of each analgesic class are compared, and results are displayed. The assumptions of normality and equal variance are met.

a. Antidepressant Users

A total of 14,708 (36.8%) patients used antidepressants persistently compared to 25,298 (69.1%) patients who were non-persistent users (Table 5-13). Persistent antidepressant users were younger than non-persistent users, with mean ages (SD) of 62.8 (13.6) years and 68.5 (12.8) years, respectively ($p < 0.0001$). More than half of persistent users (52.5%) were between 40 and 64 years old (7,729/14,708), and females constituted the majority, with 10,553 (71.8%) of total persistent users, while 4,155 males constituted 28.2% of persistent antidepressant users within the first year of being prescribed antidepressants. Within the younger age group (<40 years), the proportion of persistent users was higher than the proportion of non-persistent users (550 vs 378 persistent and non-persistent users, representing 59.3% vs 40.7% of total <40 years old).

The median total dose in DDD received by persistent users was significantly higher than the dose received by non-persistent users, at 364 DDD/patient per year compared to 28 DDD/patient per year used by non-persistent users

(p<0.0001). There was a statistically significant difference in the number of prescriptions received by persistent and non-persistent users (12 prescriptions (IQR 8, 14) compared to 2 prescriptions (IQR 1, 6), respectively).

Table 5-13 Characteristics of Antidepressant Users by Persistence of Use

Number of Patients n= 39,906 (% From Total Users)	**Pattern of Use**	
	Persistent	Non-persistent
	14,708 (36.8)	25,198 (69.1)
Demographic and clinical characteristics (% of total respective use pattern)		
Mean age, years (SD)	62.8 (13.69)	68.5 (12.82)
<40	550 (3.7)	378 (1.5)
40–64	7,720 (52.5)	8,726 (34.7)
65–80	4,518 (30.8)	10,873 (43.1)
>80	1,920 (13.0)	5,221 (20.7)
Gender (% of total respective use pattern)		
Males	4,155 (28.2)	8,167 (32.4)
Females	10,553 (71.8)	17,031 (67.6)
Comorbidity	4,135 (28.1)	4,346 (17.2)
Prescription data		
Amount of antidepressants DDD/patient/year Median (IQR)	364 (266.6,462)	28 (8,74)
Median number of prescriptions per year (IQR)	12 (8,14)	2 (1,6)

DDD: defined daily doses; IQR: inter quartile range SD standard deviation

b. AED Users

Persistent users were younger at the start of AED usage (mean age 62.9 (SD 13.0) years compared to 69.0 (SD 12.4) years). Nearly half (49.6%) of the persistent users were between 40 and 64 years old (1,565/3,157). Approximately 22% of all females with an incident diagnosis of KOA were

persistent AED users within one year after their first prescription (1,917/8,697), while 27.2% of total males were persistent users (1,240/4,560). There was no difference in gender distribution with regard to persistence of use (Appendix 7). Persistent users used AED doses more than 10 times higher compared to non-persistent users, with medians of 296.3 DDDs (IQR 222.6,400) and 28 (10,8.8) DDDs, respectively.

c. Opioid Users

Opioids were the most frequently prescribed analgesic class, prescribed for 70.2% of those with an incident diagnosis of KOA (75,977/108,221). However, compared to other analgesic classes, a smaller proportion of users used opioids persistently within one year following their first prescription (14.9% of users, compared to 36.8% for antidepressants, 23.8% for AEDs and 27% for NSAIDs). Consistent with antidepressants and AEDs, nearly half (46.5%) of the persistent users were between 40 and 64 years old (n=5,271 patients), and within the youngest age rank, the proportion of persistent users was almost double that of non-persistent users (2.3% of persistent users were <40 years old, versus 1.2% of non-persistent users) (Appendix 7).

d. NSAID Users

Persistent NSAID users were slightly younger, used higher cumulative doses and received more prescriptions for NSAIDs during the first year after their first prescription compared to non-persistent users (Appendix 7). There was no difference in gender distribution or comorbidity prevalence between persistent and non-persistent NSAID users.

e. Paracetamol Users

Compared with users of other analgesic classes, persistent users of paracetamol were older, and both more likely to be females and to have at least one comorbidity at baseline compared to non-persistent users ($p<0.0001$). Persistent users received a median of 233.3 DDDs during the first year after their first prescription – which was significantly higher than the median dose of 33.3 DDDs used by non-persistent users during the same period – and received a higher number of prescriptions over the same period in time compared to non-persistent users (Appendix 7).

5.5 Discussion

5.5.1 Main Findings

This study described a one-year treatment course following initial analgesic prescription and determined the proportion of persistent users within each analgesic class. The proportion of persistent users varied across classes, with the highest found among the antidepressant users (36% of total antidepressant users), while the lowest was among opioid users (15% of total opioid users). More than half of the opioid users (52.6%) were in the low cumulative dose category (<30 DDD/year), compared to 39% of AED users, 33% of antidepressant users and 26% of NSAID users.

Surprisingly, opioids (which are suggested by treatment guidelines if alternative prescribing strategies have not provided adequate pain control or were inappropriate) were more frequently prescribed than NSAIDs and paracetamol (which are recommended as first- and second-line analgesics) (NICE, 2014). The proportion of patients prescribed were 70.2%, 49.7% and 60.3% of opioids, NSAIDs and paracetamol users, respectively (n=75,977, 53,809 and 65,350, respectively, during follow-up).

Antiepileptic drug users received a median of 131 (IQR 58,309) prescriptions during follow-up, which was the highest across studied analgesic classes, and this is unlikely to be for epilepsy indications, as only 5.6% had a record of epilepsy diagnosis within a year of KOA diagnosis.

5.5.2 Comparison with Existing Literature on Persistent Drug Use

In this section, findings from the present study are compared with findings from studies of patients with CNCP conditions.

The present study found that 14.9% of new opioid users used them persistently during the first year following initiation. This was consistent with findings reported in a study including non-cancer patients who were new opioid users in 2011, in which the proportion of long-term recipients during the year following initiation was 18.3%, and ranged between 16.0% and 19.3% across geographical regions within the USA (Mosher et al., 2016). However, the proportion of persistent opioid users reported in the present study was higher than that reported in a study in Norway, which included adults with chronic non-malignant pain, in which 10% of total opioid recipients were persistent users (44,867/433,552) in 2005 (Mellbye et al., 2016). The study measured the prevalence of persistence within a specific calendar year, i.e. in 2005, and not in relation to patient time, possibly resulting in underestimation of the proportion of persistent users. Additionally, the study by Mellbye et al. (2016) included patients with chronic non-cancer pain, which implies the inclusion of patients with a variety of painful conditions, and with possibly variable severity, leading to differences in analgesic requirements. In contrast, the present study included a population of patients with a specific diagnosis, and assessed the pattern of analgesic use around the date of recorded diagnosis (Mellbye et al., 2016).

The present study showed that 27% of NSAID users were persistent users, which is higher than the 14.8% long-term use reported in an Australian

study. This difference is possibly explained by the difference in the study population, setting and the definition of long-term use. The Australian study included participants from residential aged care facilities who were older (median age of 87 (IQR 81, 91) years in females and 84 (IQR 77, 90) years in males) than the population within the present study, with a mean age of 64.6 years (SD11.26). Residents of aged care facilities are at increased risk of adverse events from NSAIDs due to their age and multiple comorbidities (Lind et al., 2019). Additionally, long-term NSAID use was defined as the continuous use of any NSAID (including topical preparations) for at least two weeks. These factors may have resulted in studying different populations and measures, hence leading to differences in the observed patterns.

Across analgesic classes, persistent users were significantly younger than non-persistent users, apart from persistent paracetamol users, who were older than non-persistent users. Within each analgesic class, the highest proportion of persistent users was between 40 and 64 years old; in contrast, persistent paracetamol users were predominantly between 65 and 80 years old. Paracetamol was for a long time perceived as the safest analgesic option, particularly among the oldest patients, and is recommended as the first-line drug in the pharmacological management of KOA (NICE, 2014). Having said that, recent evidence (Roberts et al., 2016, Conaghan et al., 2019a, Leopoldino et al., 2019) suggests a number of adverse events associated with the use of paracetamol, including all-cause death (de Vries et al., 2010), (Lipworth et al., 2003), cardiovascular (de Abajo et al., 2014) and GI (García Rodríguez and Hernández-Díaz, 2004) adverse events.

The prevalence of comorbidities was higher among persistent users than non-persistent analgesic users. This finding is consistent with other studies, where a chronic opioid prescribing pattern was significantly associated with a higher Charlson comorbidity index compared to acute opioid use patterns, with a reported OR (95%CI) of 1.12 (1.01, 124) (Hooton et al., 2015).

Persistent users received a significantly higher number of prescriptions across all classes, which was an expected finding. The number of opioid prescriptions was consistent with findings from previous research. For example, in the present study the median number of prescriptions for persistent opioid users was 14 (IQR11, 19), whereas for persistent users it was 2 (IQR 1, 6). The corresponding figures reported in a study from Norway were 13 (9–20) and 1 (1,3) (Svendsen et al., 2012).

5.5.3 Comparison with Existing Literature on Cumulative Doses

More than half of users within each analgesic class (apart from opioids) had prescriptions distributed in at least three out of the four quarters of the year. However, only between 17.5% and 36% used cumulative doses exceeding 180 DDDs within the first year after initiation. This indicates continuity and spread of analgesic use throughout the first year after initiation of new analgesic prescriptions, albeit at low doses. Similarly, increased high cumulative yearly opioid doses were also reported in the US, and were attributed to the increase in the number of days supplied, rather than dose per day (Sullivan et al., 2008).

In fact, analgesic doses within and across classes were mostly within the lower cumulative dose category (<30 DDD per year) or the intermediate cumulative dose category (30–90 DDD per year). For example, the proportion of low cumulative opioid dose users was most prominent (45.9% of all opioid users) compared to the proportions prescribed intermediate, high and very high cumulative opioid doses (25.6%, 13.5% and 15%, respectively). This could be explained by the high prevalence of weak opioid prescribing for patients with KOA, as 77.8% of all opioid prescriptions were for weak opioids during the first year after the initial prescription. The higher prevalence of weaker opioid prescribing in primary care was also reported in a cross-sectional population-based study on opioid utilisation in 111 UK primary care practices (Foy et al., 2016). The proportion of all patients (n=781,528) prescribed a weaker opioid was 12.4%, compared with 0.83% who were prescribed a stronger opioid in 2012.

Unlike opioids, a third of NSAID users (n=17,564, 32.6%) were prescribed an intermediate cumulative dose (30–90 DDD per year) and not the low cumulative dose. The reason for that can be explained by their administration regimen. Although NSAIDs are largely administered on an “as-needed” basis, they may be prescribed using dosage forms representing their DDDs. For example, the recommended dose for diclofenac sodium for chronic pain in adults is 100mg once a day, which is also the DDD of diclofenac. Hence, even on an as-needed basis, intermediate cumulative doses were achieved.

The median (IQR) number of days of NSAID exposure was reported as 476 days (182,937) (Lind et al., 2019), while the current study reported a median of 112 (30, 462) days. The difference in findings may be attributable to the included NSAID formulation, as the Australian study included both topical and oral dosage forms, whereas the present study included only the oral dosage forms of NSAIDs. Topical preparations were probably administered over longer periods for pain management among the elderly care home residents, as a safer option compared to oral preparations (Lind et al., 2019).

Among paracetamol users, almost equal proportions of low and intermediate cumulative doses were prescribed, representing 32.6% and 30.2%, respectively (n=21,322 and 19,713, respectively). Paracetamol doses included in observational studies were reported as daily doses in milligrams, rather than DDDs. The commonly prescribed daily doses in previous studies were ≤3000 mg or ≥3000 mg, as reported in a recent review (McCrae et al., 2018). Given that the DDD for paracetamol is 3000mg, the present study reports that 30.2% of the patients used 3000mg daily for up to 3 months within a year following initiation.

Within antidepressant users, 36.9% used the very high DDD per year cumulative dose category, whereas 33% used the low dose category. The use of very high doses was largely driven by the fact that 60% of SSRI and 62% of SNRI users had used cumulative doses exceeding 180 DDD per year. The prevalent use of SSRIs probably reflects its being prescribed for the management of depression, which is a common comorbidity among

patients with KOA. SSRIs are recommended as the first-line antidepressants for the management of major depressive disorders in adults, in accordance with the national clinical guidelines (NICE, 2018).

Those using the low-dose category within antidepressants mostly used TCAs (55% of all low-dose users). Amitriptyline (one of the TCAs) is recommended as first-line therapy for neuropathic pain (NICE, 2018a), and may therefore be used by patients with KOA for that role. Lower DDDs per year within the TCA subclass can be explained by the fact that the unit of measure (DDD) is based on the main indication of the drug (WHO, 2018), which is depression in the case of antidepressants. However, doses prescribed for pain management are usually lower than those used for the management of depressive illnesses. For example, the DDD for amitriptyline is 75mg, which corresponds to the maintenance dose for depression for an adult, while the dose for pain is much lower and ranges between 10mg and 25mg daily (Kamble et al., 2017).

5.5.4 Strengths and Limitations

This study has a number of strengths. It included all patients with an incident diagnosis of KOA, which avoids selection bias, since it ensures that the included patients were at a similar level regarding OA-related pain and severity of symptoms. Although pain severity is not recorded in CPRD data, the included patients are likely to have experienced similar degrees of pain. Research showed that receiving a diagnosis of OA in primary care was

influenced by the presence of risk factors (e.g. old age) and interfering pain. The reporting of interfering pain was associated with a recorded OA diagnosis (OR [95% Credible Interval CrI] 1.45 [1.09,1.92]) rather than a recorded peripheral joint symptom's diagnosis (Jordan et al., 2016). This implied that patients with a recorded diagnosis of OA exhibit similar pain characteristics. It would be reasonable, therefore, to assume that patients within the present study had experienced the same level of pain (as they all had a recorded KOA diagnosis), which minimised the potential of selection bias.

This study inclusion criterion differed from several other studies which have included patients with CNCP, which implied the inclusion of multiple diagnoses for which opioids were prescribed (Svendsen et al., 2012, Mellbye et al., 2016).

Unlike former studies, which defined and measured persistence during a particular calendar year (Svendsen et al., 2012), persistence in the present study was measured during a clinically relevant period (one year from the first prescription, i.e. the first patient year of treatment). Previous studies have suggested that long-term receipt patterns are established in the first year following initiation (Vanderlip et al., 2014). A total of 82.5% of a national sample of US veterans receiving long-term opioid therapy remained long-term users even after 3.5 years of follow-up (total n=550,616 patients). Determination of the proportion of persistent users within one year after initiation of each of the five analgesic classes enabled the characterisation of a group of patients that may potentially continue such a pattern over many

years. Such patients (persistent users), particularly persistent opioid and AED users, require closer monitoring to detect potential problematic drug-use disorders.

Unlike previous studies measuring persistence of analgesic use while capturing either duration of use or dose level, the present study defined persistence using a method that incorporated two attributes of persistent use: the duration of use, measured as the generation of at least one prescription within each of three quarters of the year, as well as the intensity of use of analgesics during that interval.

Measuring persistence with two attributes compared to a single one implies that those who were determined to be persistent users had really used the respective therapies persistently, which in turn increases the clinical meaningfulness of these findings and provides reassurance regarding the validity of the findings. The study also determined the extent of persistent use of each analgesic class among patients with KOA.

The results from the present study must be interpreted with due consideration of its limitations. The study assumed that antidepressants and AEDs prescribed around the date of KOA diagnosis were actually prescribed for KOA-related pain management. This assumption might have led to a misclassified estimate of analgesic exposure, and specifically, overestimated exposure estimates for the indication of KOA pain management.

The set DDD cut-off levels for persistence determination at 180 DDD provide a sensitive level for the recognition of patients who are at risk of developing adverse outcomes with the use of analgesics, or developing an overdose. Research showed that 68% of the persistent opioid users were retained over at least the subsequent two years, implying continued long-term persistent use pattern when a dose level of 180 DDD per 365 days was prescribed (Svendsen et al., 2012). In a separate study, 47% (total n=34,661) of persistent opioid users in 2005 continued the persistent use pattern in each of the subsequent six years (i.e. used ≥ 180 DDDs each year for six years). Hence, this cut-off level of cumulative annual exposure had demonstrated the ability to describe a pattern of really long-term use. Long-term use of opioids was shown to be associated with a risk of overdose and dependence/abuse (Dunn et al., 2010, Edlund et al., 2010).

However, data on the exposure levels of the remaining analgesic classes is lacking, and research is required to confirm the applicability of this level of dosing (>180 DDD/year) to predict problematic use. Socioeconomic and lifestyle factors were not included in the analysis when characterising patients with persistent use, and the included comorbidities were those which are associated with a higher risk of adverse outcomes within the population of OA patients.

More than a quarter of NSAID users were persistent NSAID users, which is likely to be an underestimation of the actual proportion, as these are accessible through OTC supply. Likewise, the proportion of persistent

paracetamol users (17.5%) is probably underestimated, due to accessibility through OTC supply.

5.5.5 Study Implications

5.5.5.1 Implications on Practice

The study found that 1 in 7 new opioid users became persistent users of opioids within the first year of initiation. Additionally, 1 in 5 AED users met the criteria of persistent use by the end of the first year after their initial prescription (14.8% and 23.8% of opioid and AED users, respectively, were persistent users). This is a clinically significant finding; it implies that within just the first year after treatment with these analgesics, a considerable proportion were persistent users, who are likely to continue such a pattern, as evident from prior opioid utilisation research (Vanderlip et al., 2014, Svendsen et al., 2012). Prescribers need to be aware/educated on such research findings, and eventually observe patients' prior opioid/AED receipt pattern through the computerised prescribing systems in the GP practices before making decisions on further prescription. This may aid clinicians in identifying and avoiding unintentional persistent use before it becomes established.

The present study has also provided information regarding the persistence of use of NSAIDs and paracetamol among patients with KOA. However, it is potentially an underestimation of true usage, due to the accessibility of NSAIDs and paracetamol as OTC preparations. The identification of such

proportions of NSAID and paracetamol persistent users (27.0% and 17.5%, respectively) warrants devoting focused attention to ways to further enforce the cautionary use of these drugs, in accordance with national guidance recommending the use of NSAIDs for the shortest possible duration, and at the minimal effective doses (NICE, 2014).

The emerging evidence on risks associated with paracetamol use is a public health issue that requires prompt intervention at various levels, including clinical practice and patient self-care, as well as regulatory levels and the pharmaceutical industry.

By describing the proportion of persistent analgesic users during the first year after initiation, this study informs policy and interventions aimed at safer use of drugs in patients with KOA.

5.5.5.2 Implications for Research

The findings from this study may have several implications for future research. The present study has established the proportion and characteristics of persistent analgesic users among patients with KOA; further research on the clinical outcomes associated with persistence of use are required to inform safer prescribing practices.

Adopting a definition that characterises persistent analgesic use with two dimensions (prescription distribution and dose level) has described persistence more comprehensively than definitions based on a single dimension. The adopted definition can potentially form a tool for objectively measuring and quantifying persistence of analgesic use in several other

chronic non-cancer pain conditions, with subsequent comparisons across other painful conditions, settings and even countries. The findings can then be studied, and optimal management strategies shared to promote optimal management.

Persistence of antidepressant and AED use has not been comprehensively described among patients with painful conditions. Hence, the findings of this study need to be validated first, before informing future research aimed at characterising exposure patterns, particularly persistence of use. This is of the utmost importance in the era of raising concerns regarding the safety of novel classes of antidepressants, such as SNRIs, and newer classes of AEDs, such as gabapentinoids (Evoy et al., 2017), (Gribbin et al., 2011). Gabapentin and pregabalin were classified as Schedule 3 controlled drugs in April 2019. This means that there is greater restriction on the prescribing and dispensing of gabapentinoids in the UK, where doctors are required to physically sign prescriptions, and pharmacists must dispense the drugs within 28 days of the prescription being written (NHS, 2019). The identification of persistence patterns within analgesic classes other than opioids (including NSAIDs and paracetamol) informs practitioners of the exposure levels of these drugs, and may also be the foundation for drawing cut-off cumulative dose limits to guide safer prescribing of these analgesics in future.

5.6 Conclusion

Among primary care patients with KOA, analgesics were frequently initiated at low cumulative dose levels (<30 DDD/year) or intermediate cumulative dose levels (30–90 DDD/year). However, between 14.9% and 36.8% became persistent users of the respective analgesic by the end of the first year after their initial prescription.

Persistent users were significantly younger than non-persistent patients across all classes apart from paracetamol. Persistent analgesic users were issued more prescriptions and used significantly higher doses of analgesics compared to non-persistent users.

Chapter 6 Exploratory Study of Fall Event Recording in Patients with Knee Osteoarthritis Using Clinical Practice Research Datalink and Hospital Episode Statistics Linked Data

6.1 Introduction

Several studies showed that analgesic use was associated with adverse outcomes in older adults due to factors such as ageing, high burden of comorbidities, and polypharmacy (Dhalwani et al., 2017, Field et al., 2004). Additionally, analgesics including opioids, as well as antidepressants and AEDs, cause acute central nervous system (CNS) effects such as sedation and dizziness, which can manifest as derangements of balance and gait, hence constituting risk factors for serious outcomes such as falls in older adults (Darowski et al., 2009). However, patients with KOA may be at increased risk of these adverse outcomes, particularly falls, precipitated by additional contributing risk factors including joint pathology and instability and KOA-related pain (Arden et al., 2006, Stubbs et al., 2014).

Falls are a major public health concern in the UK and many countries around the world, especially those with ageing populations (WHO, 2007). Although the use of analgesics including antidepressants was identified as a risk factor for falls among older patients (aged ≥60 years) (Darowski et al., 2009, Seppala et al., 2018c), this association is less well described in patients with KOA who use analgesics. Moreover, population-level data on analgesic use and risk of falls in patients with KOA in the UK is scarce.

Therefore, the present research project aimed at examining the association between analgesic use and the risk of falls in patients with KOA. However, in order to obtain accurate estimates, it was important to ensure the selection of an adequate data source to maximise the capture of fall events. Consequently, the work within this chapter explored and compared fall recording in CPRD and CPRD–HES-linked data, to inform the data source for further studies of this research.

6.1.1 Rationale for Selection of linked CPRD-HES data for falls

Falls are mostly managed in primary care settings, where patients usually present following a fall. However, up to 5.3% of the UK population aged 60 years or over attend accident and emergency (A&E) departments with fall-related injuries, and up to 31% of them are hospitalised, resulting in the high cost implication of £1 billion (Scuffham et al., 2003).

Patients with KOA who experience fall events resulting in injuries such as hip fractures may be hospitalised without necessarily presenting in primary care. Secondary care encounters are recorded in primary care records; however, a delay is expected, due to the need to feed this information into primary health records. Analysis of such events and their possible management in either primary or secondary care, or in both (depending on the event's severity), will benefit from using primary care data linked to secondary care data (Rothnie et al., 2016).

Record linkage between CPRD and Hospital Episode Statistics (HES) will potentially allow for the identification of patients who sought medical care for falls in a hospital setting, or patients who were referred to a hospital for an injurious fall, while their CPRD records have not been updated as a result of delays in the manual input of hospital discharge summaries and referral notes into GP systems.

The potential benefits of record linkage in maximising the capture of fall events in patients with KOA are unclear. Previous work on the utility of record linkage used data from primary care (CPRD), hospitalisation records (HES), and mortality records from the Office of National Statistics (ONS data) to measure the incidence of injury (poisoning, fractures and burns) among children and young people (Baker et al., 2016). The study reported that falls were the most common mechanism for fractures, recorded in 50% of the cases with a recorded mechanism (n=2,650 fractures). However, this study determined the epidemiology of injury in children and young people aged between 0 and 24 years in England, and did not report the proportion of falls identified in each data source separately (Baker et al., 2016). Therefore, the extent of overlapping of fall recording between the CPRD and HES is unclear, and it is not known whether there is a considerable proportion of falls being recorded only in HES.

6.1.2 Evidence on the Importance of Records Linkage

Healthcare in the UK is mainly delivered by the National Health Service (NHS), a public health care system. The majority of the UK population are registered with a GP, and GP records are the patients' primary medical records. Data is collected as part of routine primary-care clinical practice, and to ensure continuity of care, with details of secondary-care encounters (e.g. hospital admission/care) routinely communicated to an individual's GP practice. However, delays and under-recording or inaccurate recording are possible, as this data is manually fed into the GP systems (McDonald et al., 2018). Consequently, a number of studies have reported suboptimal recording of secondary care events in primary care records; for example, 21% of myocardial infarctions (MI) and 80% of clinically relevant bleeding events occurring in the hospital and recorded in the linked datasets did not appear in primary care records (Herrett et al., 2013, McDonald et al., 2018). Findings from these studies suggested the use of linked data (CPRD linked with external datasets) to combine information from different sources, and provide more complete and comprehensive information on all health events and encounters.

Since October 2008 it has been possible to link CPRD to external datasets through a trusted third party. CPRD-linked datasets include Hospital Episode Statistics (HES), the National Cancer Data Repository (NCDR), the Myocardial Ischaemia National Audit Project (MINAP), and the ONS. The added value of linked data over single source data in estimating accurate incidence and prevalence of diseases was proved for several conditions,

including infectious conditions such as community acquires pneumonia (CAP) (Millett et al., 2016) and cardiovascular events (Herrett et al., 2013).

For example, Millet et al. (2016) reported that the identification of population-averaged incidence estimates of CAP over the period from 1997 to 2010 were 39% to 83% higher using primary–secondary care linked data compared to standalone primary care data. In another study, Harrett et al. (2013) found that there was a significant improvement in the crude incidence of acute MI using linked national health care sources – CPRD, HES and MINAP – with single sources underestimating the crude incidence of acute MI by 25% to 50% compared to the use of the entire linked sample (Herrett et al., 2013).

Records linkage is also important because cases identified using CPRD can differ from those identified in secondary care in demographic and clinical characteristics. Patients with acute MI identified from HES or disease-specific registries were found to be (on average) older, less likely to smoke, and more likely to be from the least-deprived quintiles, compared to those identified only in CPRD (Herrett et al., 2013). CPRD records identified almost three times higher comorbidity prevalence than HES data in a study including 657,264 patients, where 189,763 (28.8%) patients with at least one morbidity were identified from CPRD, compared to 84,217 patients (12.8%) from HES (Crooks et al., 2012). This difference in comorbidity recording was explained by the fact that primary care data provides continued (longitudinal) clinical histories for the entire population, in contrast to the secondary care data, which provides snapshots of clinical

histories for a subset of admitted patients and may not contain comprehensive information on comorbidities (Crooks et al., 2015).

Additionally, records linkage is paramount when estimating the risk of certain outcomes, such as mortality. In the study by Herrett et al. (2013) the immediate all-cause mortality and mortality at one year were estimated among patients with an acute MI recorded in CPRD, HES and the MINAP databases. The risk of immediate mortality was highest in patients with acute MI recorded only in CPRD, while mortality rates at one year were similar in CPRD, HES and the disease registry (MINAP) cohorts. The reason for the difference in mortality was that primary care data included records of patients who did not reach hospital, and hence were not recorded in the HES or MINAP databases. In another study, the risk of 28-day case fatality was twice as high in cases of upper gastrointestinal bleeding defined only in hospital data, compared to those defined only in CPRD (13.1% (95% CI 12.7%–13.5%) vs 7.7% (95% CI 7.4%–8.1%) respectively) (Crooks et al., 2012).

The role of record linkage in evaluating patient outcomes is of particular importance given that the NHS is now legally required to evaluate patient outcomes, such as reducing premature mortality from the major causes of death (e.g. cardiovascular disease, lung disease, liver disease and cancer) through timely and effective health care (DH, 2013). It is anticipated that in the future, other outcomes may be considered (e.g. falls).

In summary, the importance of record linkage, particularly between primary care (e.g. CPRD) and hospitalisation records (e.g. HES) has been acknowledged by researchers, as well as policy makers, with regard to deriving accurate estimates of outcomes. Given the importance of record linkage demonstrated in several clinical conditions, the present study sought to examine the influence of record linkage on the number of falls identified from the CPRD and HES databases. Results will subsequently inform the decision on data source selection to estimate fall risk among analgesic users compared to non-users during the first year after diagnosis of KOA.

6.2 Study Aim and Objectives

The study was devised to determine the proportion of patients with a fall recorded within one year of KOA diagnosis within CPRD or HES, or both databases, using CPRD–HES-linked patient data.

The specific study objectives were:

1. Determine the number and proportion of primary care patients, with an incident diagnosis of KOA, who had a recorded fall within one year of KOA identified only in CPRD or HES, or in both databases.
2. Compare the first fall dates documented in both databases for patients having records of falling in both databases (CPRD and HES).

6.3 Methods

To determine the proportion of patients with a recorded fall within the hospitalisation records, the study used data from linkage-eligible patients. Details of HES data files were presented in Chapter 2.

6.3.1 Study Population and Follow-up Time

The overall study population constituted patients with an incident diagnosis of KOA recorded in CPRD clinical or referral files between 1st January 2000 and 31st December 2014 who were aged 18 years or older. Of the patients with an incident diagnosis of KOA, this study used the data of the CPRD patients who were registered with practices which had consented for linkage. The HES-linked data was used for the main analyses.

The follow-up period started from the date of incident diagnosis of KOA (index diagnosis). The end of the follow-up period was the earliest date of the following: date of death, transfer out date, the practice's last collection date, or the end of study follow-up period on 31st December 2015. The follow-up end date (31st December 2015) was selected to ensure at least a one-year follow-up period. Patients who had their incident diagnosis after 31st December 2014 were not included in this study.

6.3.2 Definition of Fall in CPRD and HES

Fall events were identified with appropriate Read and ICD-10 codes. In CPRD a patient had a fall if a Read code for fall was recorded within the

clinical or referral files. The Read code list was developed from the CPRD code browser, and compared with a list from a published study for falls obtained through correspondence with the first author (Li et al., 2013). A final list was generated by combining the codes from both lists after removing duplicate codes. Patients who had a hospital episode related to falling in HES admitted patient care (APC) records were identified using corresponding ICD-10 codes which were adopted from previous research (Chen et al., 2016) and published on the WHO webpage (WHO, 2016). Only the first recorded fall was assessed during the period of one year after the diagnosis of KOA; all subsequent falls were excluded.

Within HES data, the date of the first episode of care overseen by a healthcare professional was selected to represent the date of fall. Read codes and ICD-10 codes are presented in Tables 3.1 & 3.2 in Appendix 3.

The period of one year after KOA was selected to examine the association; this was based on evidence which showed that patients may discontinue, augment or switch treatments within the first year of treatment (Gore et al., 2012). Previous research also showed that the risk of fall is greater within one month of antidepressant initiation (Coupland et al., 2011). Capturing analgesic prescribing prevalence within the first year would also present important information on the number and types of different analgesics used by individual patients within this time frame.

6.3.3 Outcome Measures

6.3.3.1 Number and proportion of fallers in CPRD, HES or both

Within the period of one year of index KOA diagnosis, the study identified the number and proportion of patients with a record of falling in CPRD, HES or both, and patients were grouped accordingly. The operational definition and the corresponding practical definition along with the resulting patient group are presented in Table 6-1. The stepwise process of deriving these patient groups is outlined in Figure 6-1.

Table 6-1 Operational and Practical Definitions of Patient Groups According to Fall Records in CPRD, HES or Both Databases

Operational Definition	Practical Definition of Patient Group	Patient
Patients who had a fall recorded only in CPRD (no fall recorded in HES data)	Those who had no hospitalisation record for fall, i.e. were presented and managed only in primary care	Group 1
Patients who had a fall recorded only in HES data (no fall recorded in CPRD)	Those who only have hospitalisation records, i.e. were hospitalised straight without presentation in primary care	Group 2
Patients who had a fall recorded in both CPRD and HES data	Those who had both a primary care and hospital record of fall, i.e. initially presented in primary care and were then hospitalised, or hospitalised, then records fed into GP system	Group 3
Patients who had no fall record in CPRD or HES data	Non-fallers in both databases: no GP record or hospitalisation record for fall	Group 4

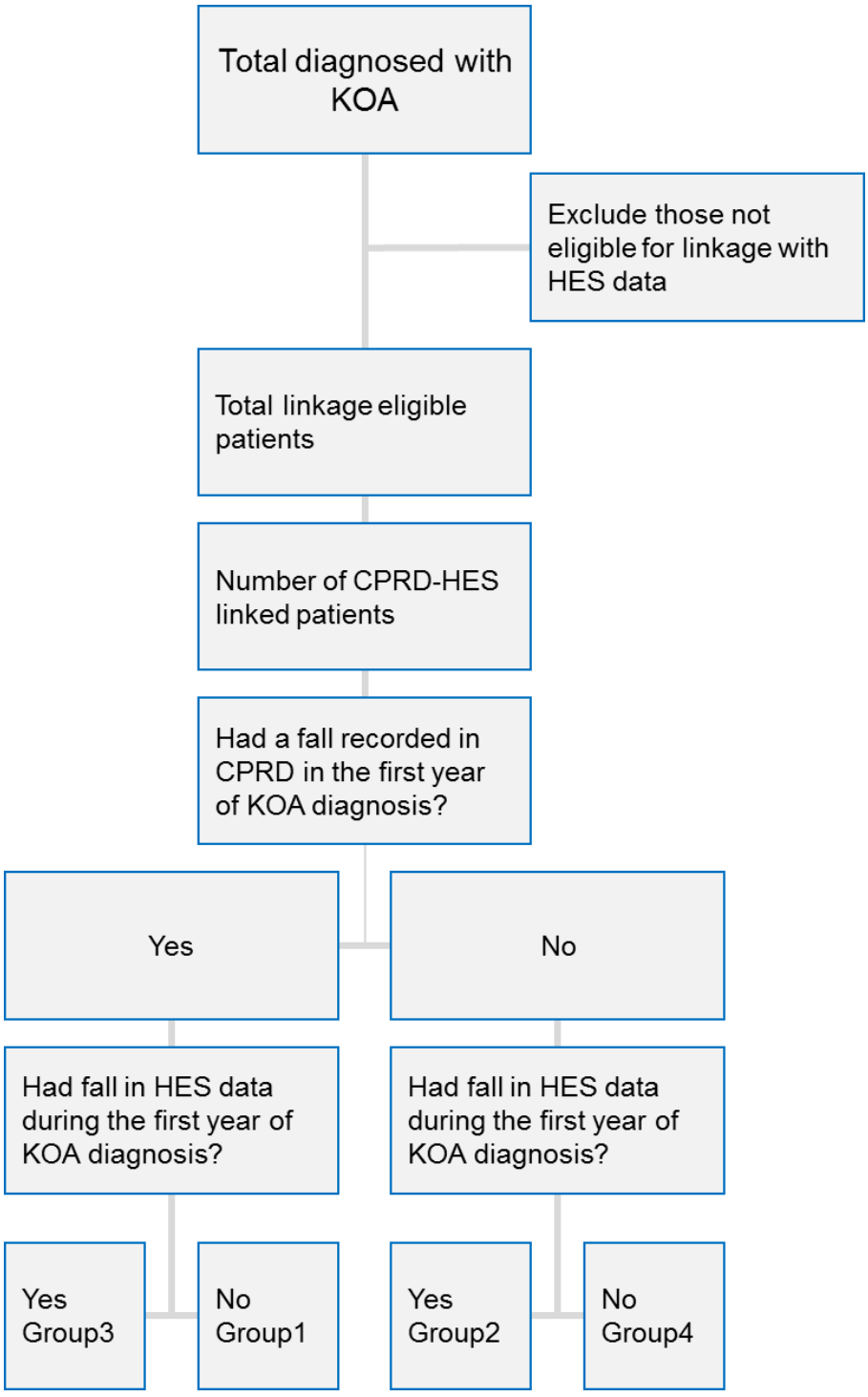


Figure 6-1 Flow Diagram Outlining the Process of Patient Group Identification According to the Existence of Fall

6.3.3.2 Time Gap between Fall Recordings

For patients in Group 3, i.e. those who had a record of falling during the first year after KOA diagnosis within both databases, the date of first fall recording was identified, and the gap in days between the two dates was determined. Patients were grouped and categorised according to the gap (number of days) between the two dates, as presented in Table 6-2. These definitions were adopted from previous work on the incidence of falling in primary care (GRIBBIN, 2013).

Table 6-2 Time Gap between Fall Recording Dates in CPRD and HES Datasets: Category and Definition

Time Gap Category	**Definition**
No gap	fall events in CPRD and HES were recorded on the exact same date
Very short gap	fall dates in CPRD and HES were within 2 days of one another
Short gap	fall dates in CPRD and HES were within 7 days of one another
Intermediate gap	fall dates in CPRD and HES were within 14 days of one another
Long gap	fall dates in CPRD and HES were within 30 days of one another
Prolonged gap1	fall dates in CPRD and HES were within 60 days of one another
Prolonged gap2	fall dates in CPRD and HES were within 90 days of one another
Prolonged gap3	fall dates in CPRD and HES were over 90 days apart

6.3.4 Data Management

The HES files were provided in .txt format and were imported into a statistical software package (STATA 15.2) for further analysis. The records were checked for inconsistencies in dates; for example, discharge date before admission date or episode start date after discharge date were identified and dropped.

6.3.5 Statistical Analysis

Descriptive analysis of demographic and clinical characteristics of the study population was performed.

6.4 Results

6.4.1 The whole Study Population

Out of the 108,221 patients with an incident diagnosis of KOA in CPRD, who constituted the overall population of KOA (as detailed in Chapter 3 of this thesis), a total of 4,139 were excluded from this analysis because their first KOA diagnosis in CPRD was after 31th December 2014.

The remaining 104,082 patients from 660 practices across the UK constituted the study population (the whole study population which was selected from CPRD standalone data). A total of 45,678 patients were aged 40–64 years at the start of follow-up (43.9%), while 40,305 (38.7%) of them were aged 65–80 years. Females constituted 58.7% of the study population (n=61,057) (Table 6-3).

6.4.2 HES-Linked Population

Of the 502 English practices, data from all 390 HES-linked practices was used. The linkage between CPRD and HES was over the period from 1st April 1997 to 31st August 2017. A total of 59,737 patients diagnosed with KOA were eligible for linkage from the 390 consenting English practices; 2,354 (3.9%) of them were excluded due to missing discharge dates or having inconsistent dates (episode start date later than discharge date, or episode start date later than episode end date). This yielded 57,383 HES-linked patients for further analyses, representing 55.1% of the total patients with a diagnosis of KOA. The demographic and socioeconomic characteristics of the HES-linked patients were largely similar to those of the whole study population (Table 6-3).

Table 6-3 Characteristics of the Study Population

	Whole Study Population	**HES-Linked Patients**
Number of patients	104,082	57,383 (55.1%)
Gender		
Males	43,025 (41.3%)	23,352 (40.7%)
Females	61,057 (58.7%)	34,031 (59.3%)
Age in years*		
Mean (±SD)	66.30 (±12.76)	67.04 (±12.82)
Range	(18.03-106.37)	(18.03-104.72)
Age ranks, years (% from total)		
<40	2,143 (2.1%)	1,157 (2.0%)
40-64	45,678 (43.9%)	23,766 (41.4%)
65-80	40,305 (38.7%)	22,790 (39.7%)
>80	15,956 (15.3%)	9,670 (16.9%)
IMD score (% from total)		
1 (least deprived)	14,176 (21.6%)	12,100 (21.9%)
2	15,456 (23.5%)	13,425 (23.4%)
3	13,842 (21.2%)	12,153 (21.2%)
4	12,610 (19.2%)	11,062 (19.2%)
5 (most deprived)	9,696 (14.8%)	8,620 (15.0%)

* calculated at KOA diagnosis; SD – standard deviation; IMD – index of multiple deprivation

6.4.3 Proportion of Patients with a Recorded Fall in CPRD, HES or Both

Using CPRD standalone data, the whole study population consisted of 104,082 patients, and **3,275** (3.1%) of them had a fall recorded within one year of KOA diagnosis. However, using the HES-linked population (n=57,383), the number of patients with a fall recorded within one year of KOA diagnosis was **2,384**, representing 4.1% of the total linked patients.

Subsequently, the process of identifying each of the four patient groups was followed and the results are summarised in Figure 6-2.

Within the linked population (n=57,383), the number of patients who had a fall record only in CPRD (group 1) was 1,852 (3.2%); however, there were an additional 365 (0.6%) patients who had a fall recorded only within HES data (group 2). There were 167 (0.3%) patients who had a record in both databases (group 3) (Figure 6-3).

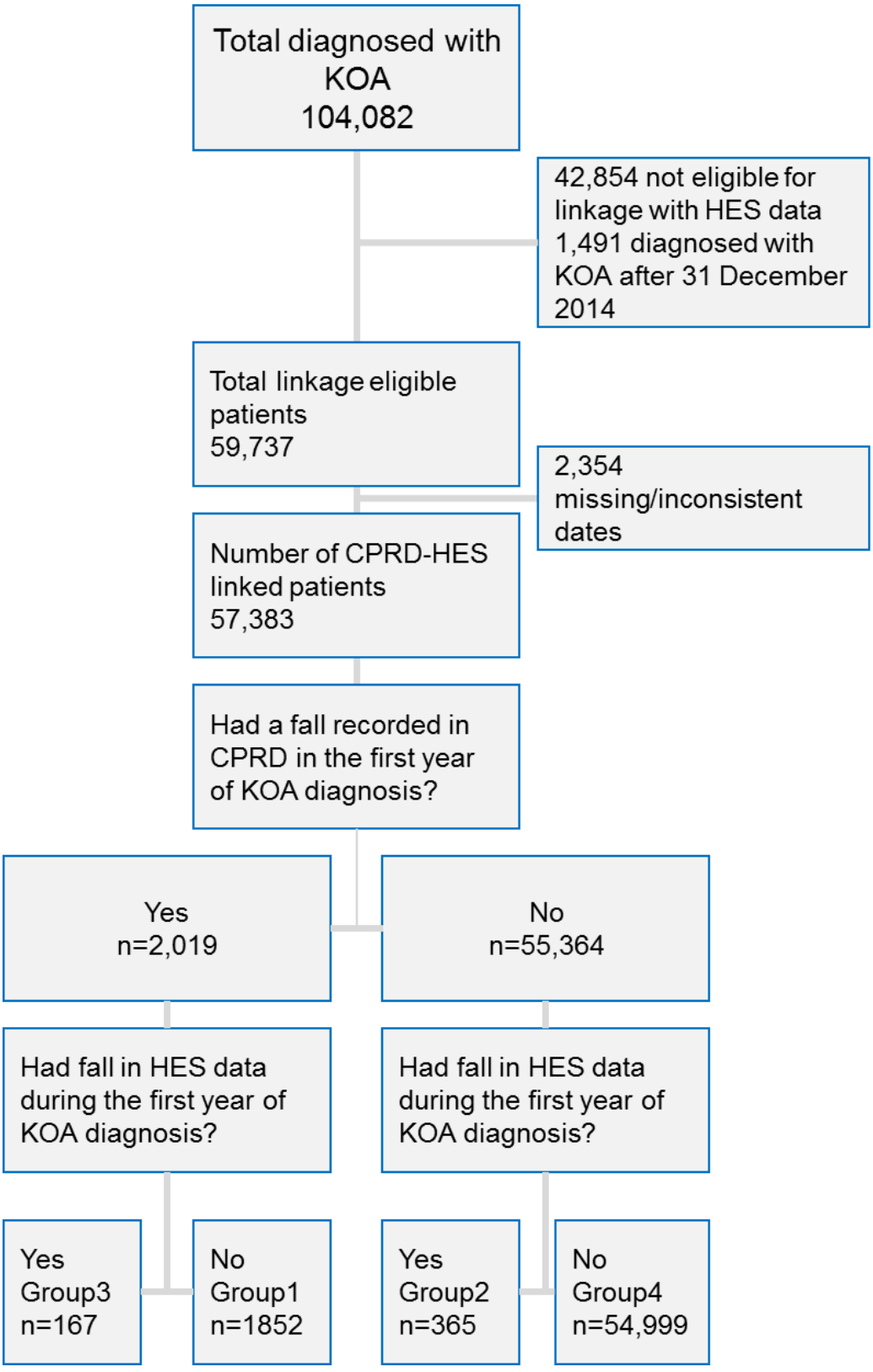


Figure 6-2 Flow Diagram Outlining the Process of Patient Group Identification According to the Existence of a Fall Record in CPRD, HES or Both.

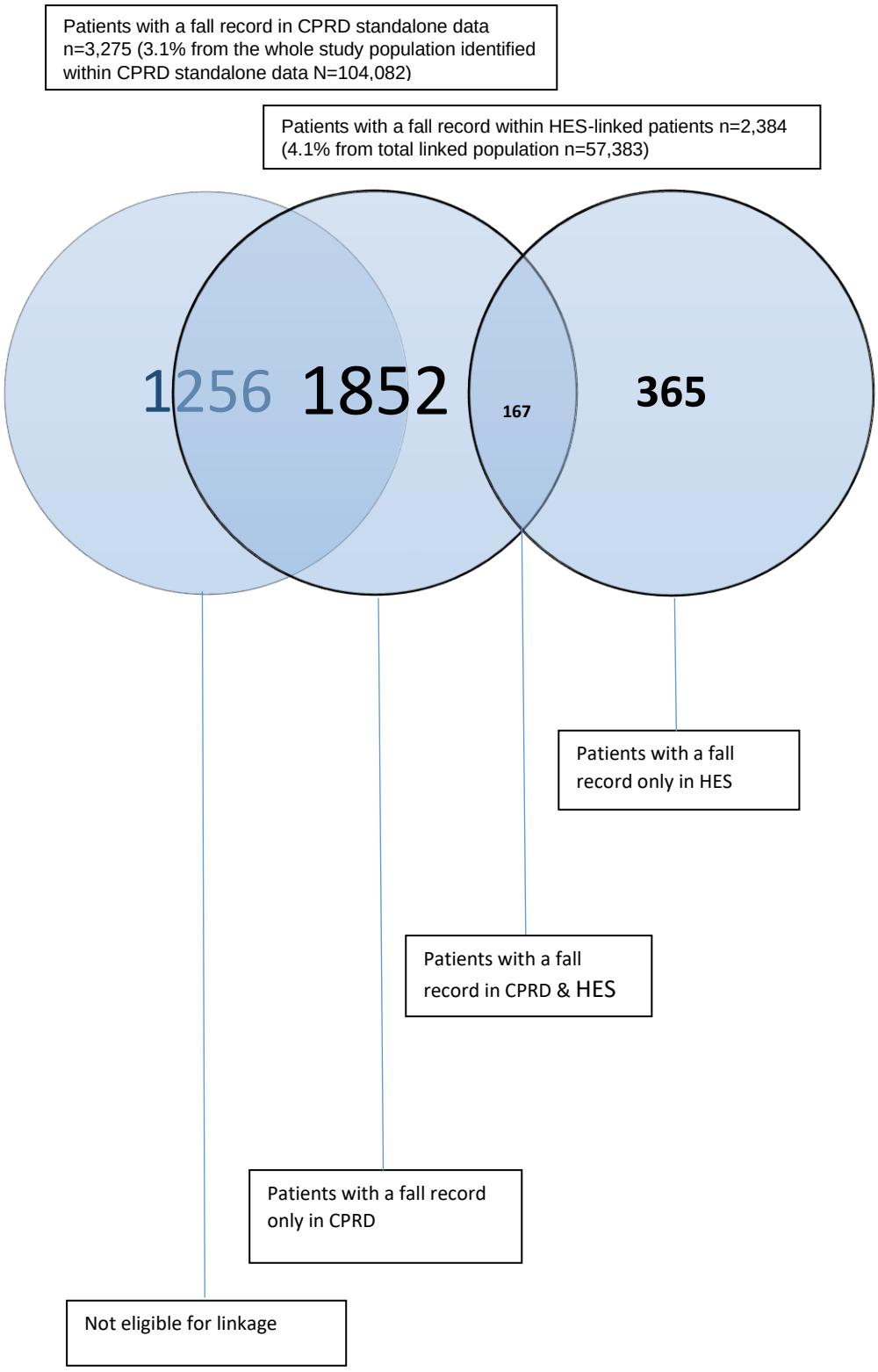


Figure 6-3 Number of Patients with a Fall Record Identified within Primary Care (CPRD Standalone Data) and Secondary Care (HES).

6.4.4 Characteristics of Patients with a Fall Record Identified in CPRD, HES or Both

The demographic, socioeconomic and clinical characteristics of patients who had a fall record identified in CPRD, HES or both databases were analysed and presented in Table 6-4.

Table 6-4 Demographic and Clinical Characteristics of Patients with Fall Records in CPRD, HES and in Both, among the HES-linked Population

Patient Characteristics	**Patients with a Fall Record Identified in Respective Database(s), n= 2,384**		
	Only CPRD	Only HES	CPRD & HES
Number of patients (%) from total	1,852 (77.7)	365 (15.3)	167 (7.0)
Females (%)	1,391 (75.1)	229 (62.7)	135 (80.8)
Age			
Mean (±SD years)	76.2 (±11.87)	76.1 (±12.26)	81.6 (±10.94)
Age range	33.1- 102.7	30.2 - 103.4	36.9 - 104.7
Age group, years			
<40	7 (0.4)	2 (0.5)	1 (0.6)
40–64	331 (17.9)	66 (18.1)	14 (8.4)
65–80	693 (37.4)	134 (36.7)	41(24.5)
>80	821 (44.3)	163(44.7)	111(66.5)
IMD Score			
1	361 (19.5)	75 (20.7)	28 (16.8)
2	430 (23.2)	91(25.1)	41 (24.6)
3	406 (21.9)	75 (20.7)	39 (23.4)
4	386 (20.9)	64 (17.6)	32 (19.2)
5	268 (14.5)	58 (16.0)	27 (16.1)
Comorbidity	433 (23.4)	58 (23.3)	38 (22.8)
FRIDs	1,398 (75.5)	261 (71.5)	132 (79.0)
Previous fall	253 (13.7)	79 (19.2)	26 (15.6)

SD standard deviation; IMD score index of multiple deprivation; FRID fall risk increasing drugs

Females constituted the majority of those who experienced a fall across the data sources, particularly among those identified in both CPRD and HES, as more than 80% (n=135) were females. Across the data sources, very old patients (>80 years age rank) constituted the highest proportion of those who experienced a fall (44.3% of total only in CPRD, 44.7% of total only in HES, and 66.5% of total in both databases). It was observed that the

proportion of very old age patients (80 years or over) represents the majority (66.5%, n=111) of patients with a fall who had a record in both databases.

6.4.5 Comparison of Dates of Fall Recording

Records of the patients who had a fall recorded in both databases (CPRD and HES) were further analysed to determine the time gap between the two dates of falling. The date of the first fall after the diagnosis of KOA was selected for the comparison, and the results are summarised in Table 6-5.

Table 6-5 Time Gap between Fall Recording Dates in CPRD and HES Datasets, Gap Category and Number of Patients in Each

Time Gap Category (Days of Gap in Recording Between CPRD and HES)	**Number of Patients with a Record of Fall (n=167)**
No gap (same recording date in CPRD and HES)	45 (26.9%)
Very short gap (≤ 2days)	19 (11.3%)
Short gap (>2 days and ≤7days)	17 (10.2%)
Intermediate gap (>7 days and ≤14 days)	9 (5.4%)
Long gap (> 14 days and ≤30 days)	16 (9.6%)
Prolonged gap 1 (>30 and ≤60 days)	15 (9.0%)
Prolonged gap 2 (>60 and ≤90 days)	7(4.2%)
Prolonged gap 3 (>90 days)	39 (23.3%)
Number of falls first recorded in HES	58 (34.7%)
Number of falls first recorded in CPRD	64 (38.4%)

Of the 167 falls, for 45 patients (26.9%) falls were recorded on the exact same date in both databases, and 61 falls (36.5%) were recorded within a month of one another (not including those recorded on the exact same date). However, 61 (36.5%) fall events were recorded with a gap of longer than a month between the two recorded dates. There were 58 patients who

had their fall first recorded in HES data with a median delay of 52 days (IQR 7,153) until it was recorded in the GP system.

For patients who had a record of fall first recorded in primary care (n=64), there was a median of 19.5 days' difference (IQR 4.5, 91) in the recording between primary and secondary care data for fall events.

6.5 Discussion

6.5.1 Main findings

This study explored fall event recording in patients with KOA within CPRD and HES, and in both databases. A total of 2,384 falls were identified within the CPRD–HES-linked data; the majority of them had a record in CPRD (2,019 falls, representing 84.6% of all falls). However, a small proportion of the total identified fall events were only recorded in HES (365 falls, representing 15% of all falls).

Among those with a fall record in both databases within one year of KOA diagnosis, fall dates were within a month for 64% of the patients, while for 23.3% there were more than 90 days between the dates.

6.5.2 Proportion of Fallers within the Whole Study Population vs HES-Linked Population

Unlike the whole study population, which included 104,082 patients with a diagnosis of KOA, who were registered with GP practices across the UK,

HES-linked practices reside only in England. Hence, the number of linked patients was approximately 55% (57,383 patients) of the total diagnosed with KOA. The proportion of patients with a recorded fall within the HES-linked population was 4.1% (2,384 falls in the 57,383 HES-linked population), and was slightly higher than the proportion within the CPRD standalone data (3.1% patients with falls recorded among 104,082 patients with KOA). Nearly 85% (n=2,019) of all falls were recorded in CPRD, while 22.3% (n=532) were recorded in HES data.

There were 1,852 patients who were identified only within CPRD (77.7% of all falls) compared to 11.1% identified only within HES. This was in line with findings from a previous study on the prevalence of injury in England among children and young people using record linkage. The study reported that 75% of total fractures were recorded only in CPRD data, compared to 8.6% recorded only in HES data (n=139,662 and 15,972) (Baker et al., 2016).

Results showed that linkage to HES data did not substantially increase the number of identified fallers; in fact, a mere 365 fall events were only recorded in HES, and would have been missed if HES records were not explored. These figures suggest a limited role for record linkage in improving the sensitivity of fall identification.

Fall events are almost entirely recorded in primary care, and even those which are directly managed in hospitals (group 2) are eventually recorded in primary care.

The substantial overlap in recording could be explained by the nature of both the KOA itself and the outcome of the fall. KOA is a chronic condition which is largely managed in primary care. It is, therefore, common that patients with KOA present, are diagnosed, investigated, followed-up and managed in primary care settings. This is reflected in the annual number of GP visits, where it is estimated that 20% of the annual GP visits in the UK are for musculoskeletal conditions, including KOA (VersusArthritis, 2019)

Patients with KOA may have frequent visits to their GPs (for follow-up of KOA or care for other comorbidities), who are likely to record encountered health events such as falls during these routine consultations (NICE, 2013a).

Falls are also largely managed in primary care settings, where primary care professionals play a critical role in the prevention and management of falls, as advocated by NICE clinical guidelines and quality standards for falls in older people (NICE, 2013a, NICE, 2015a). General Practitioners and other primary care professionals' key roles are in identifying those who have had a fall, and referring those who are at risk of falling to specialised fall prevention services, for multifactorial assessment and intervention. The components of multifactorial risk assessment and multifactorial intervention are summarised in Table 6-6.

It is clear that a substantial overlap in recording falls between CPRD and hospital records found in this study is quite likely, since both the condition

(KOA) as well as the outcome (fall event) are largely managed in primary care settings.

Table 6-6 Key Components of the Multifactorial Risk Assessment and Intervention

Multifactorial Risk Assessment Examines the Following:	**Multifactorial Intervention should:**
Fall history	Provide strength and balance training
Gait, balance mobility and muscle strength	Address home hazards
Osteoporosis/fracture risk	Correct visual risk factors
Functional ability, fear of falling	Provide education
Vision, cognition and neurological assessment	Address specific underlying medical problems
Urinary incontinence	
Home hazards	
Cardiovascular problems	
Medications	

Although record linkage has shown value in driving accurate (unbiased) assessments of incidence and prevalence of CAP in elderly people and MI events (Millett et al., 2016, Herrett et al., 2013), it should, however, be noted that these findings are likely to depend on the disease area (McDonald et al., 2018). For instance, cancer case recording between CPRD and cancer registries was found to have a high level of concordance, with >80% of cases being present in both databases (Boggon et al., 2013). This level of concordance was achieved despite cancer being managed at different care settings, and one would expect a high improvement in sensitivity with record linkage. Similarly, a high concordance between primary and secondary care records was observed in this study for the record of falls.

The limited role of record linkage in improving the sensitivity of diagnoses of conditions or outcomes largely managed in primary care settings was also suggested by researchers in primary care. Yu et al. (2018), in their work on estimating the extent of recording of OA in CPRD – using patients

who underwent a total hip replacement (THR) or total knee replacement (TKR) as the reference population – found that OA was under-recorded in CPRD, but suggested that it is unlikely that linkage to hospital data will substantially improve the number of identified patients, since it is a condition that is largely managed in general practice (Yu et al., 2018).

Record linkage is recommended in studies aiming to estimate the incidence or prevalence of diseases, particularly those which are managed in primary as well as secondary care settings. For conditions that are managed entirely in primary care, record linkage may not be necessary (McDonald et al., 2018); however, it must be explored prior to making any final decisions on the use of the HES-linked population for incidence estimation.

In this study, the existence of a fall record in CPRD, HES or both databases suggests the occurrence of falls of varying severity; for example, patients in group 3 are probably those who presented at a GP surgery, but required hospitalisation for further management of the fall they experienced. They could also be those who were hospitalised for a fall, and their GP records were updated. On the other hand, patients constituting group 2 may represent those who were hospitalised without presentation at their GP surgery, with their records not fed into the GP system, or those who have died, and hence have not returned to their GP. Such cases may represent a group of fallers who experienced a serious fall.

Group 1 represents patients who required medical attention (GP care) but were probably managed at the GP surgery, and did not require escalated care in a hospital.

6.5.3 Study Implications

6.5.3.1 Implication for Future Work of this Research

Further work of this research project is set to investigate the association between the use of analgesics and the risk of falling. Despite proportion of patients with a recorded fall identified among the whole population (CPRD standalone data) being comparable to that of the HES-linked population, the use of an HES-linked population was considered for further work. The basis for this was that fall events identified for HES-linked patients included a subset of patients for whom escalated care/hospital care was required as a result of a probable severe fall-related injury.

It will be of great interest and importance for subsequent work of this PhD project to estimate the association between analgesic use and the risk of falling while including the proportion of patients who experienced a serious fall, and not only those who experienced any fall.

6.5.3.2 Implications of Study Findings for Research in General

This study showed that record linkage has a limited role in improving the sensitivity of fall diagnosis in patients with KOA. It had demonstrated an

example of the events that are likely to be recorded completely in primary care, hence informing researchers on the completeness of primary care records for falls of patients with KOA.

6.5.3.3 Implications for Practice and Policy

Information provided by this study on the frequency of falling, and characteristics of those who experienced a fall, could be made available to inform fall risk prevention programmes about possible groups of people within those diagnosed with KOA who are most likely to experience a fall.

Falls are a growing public health challenge in the UK, which will continue to grow due to the rising proportion of older-aged patients (65 years or older) within the UK population. The most recent census in 2011 suggested that 8.7 million people in England were aged 65 years and over (ONS, 2019a). This figure is set to increase by another 2 million by 2021, by which time the over-85 years population is expected to have grown by 40 per cent, to approximately 1.7 million (Yang Tian, 2013)

In the UK, falls are estimated to cost the NHS more than £2.3 billion per year. Falls are the leading cause of injury-related hospitalisation, and exert a burden on hospital services, in terms of both A&E visits and inpatient admissions (BGS, British Geriatrics Society, 2018). Consequently, fall prevention is one of the three priorities for optimisation highlighted in the NHS RightCare Falls and Fragility Fractures pathway, in addition to detecting and managing osteoporosis and fracture risk, and optimal support

following a fragility fracture (NHS, 2017c). The RightCare pathway also contains a number of key messages for commissioners, including working towards targeted case-finding for osteoporosis, fragility and fall risk, which involves identifying those at risk of falling, and delivering appropriate intervention, e.g. medication review, strength and balance training, and multifactorial intervention for fall and fracture prevention.

Furthermore, this study has demonstrated an example of the completeness of primary care records for falls. This knowledge is essential for health services planners, commissioners and other decision makers, as CPRD data can be reliably used for service planning purposes when required.

Although CPRD can be used as a standalone data source for information on the absolute number of patients with falls requiring medical care from GPs, there were some patients (n=365) with more serious falls which required hospitalisation for more intense medical care. Observing changes in the proportion of those hospitalised following falls may inform future resource planning and hospital bed demand/allocation planning for potential fall injury-related hospitalisation. Any reduction in the proportion of those hospitalised may serve as a quality improvement indicator for fall prevention or fracture liaison services.

6.5.4 Strengths and Limitations

The study focused on a prevalent adverse outcome (falling) that has a substantial impact on patients, the health care system and the wider

community. The study used data from both primary care and secondary care, and maximised the number of identified fall cases using code lists which were applied by other researchers in published work.

However, the study has some limitations that should be mentioned. Falls identified through electronic health records (EHR) represent those for which some form of medical attention was required, hence these do not represent all falls experienced by patients. It was revealed that up to 30% of participants in a population-based survey reported at least one fall in the prior 12 months (Gill et al., 2005). Hence, compared to surveys, the number of falls within the EHR database is potentially underestimated.

This study did not include codes for fall-related injuries, resulting in possible underestimation of the true number of falls in HES data (fall events may have been coded with the resulting injury codes, rather than fall codes). Additionally, there is the potential for under- or over-estimation of falls in HES due to inaccurate coding.

6.6 Conclusion

This study has explored the potential benefits of record linkage in improving the sensitivity of fall identification. Using the CPRD–HES-linked patient data, this study found that CPRD records included approximately 84.7% of the overall falls experienced by patients within one year of their KOA diagnosis. However, 15.3% of the falls were only recorded in hospital data;

although not a substantial proportion, this represents a group of patients who probably suffered a serious event.

The study addressed the concern that EHR from one part of the health system, such as primary care, may not capture health events occurring in other parts of the system, such as hospital care, and subsequently informed further work in this research which was based on the HES-linked population.

Chapter 7 Association Between Analgesic Use and the Risk of Falls in Patients with Knee Osteoarthritis: A Crude Analysis

7.1 Introduction

Despite the high prevalence of KOA in the UK (as described in Chapter 2), and the high prevalence of analgesic use among patients with OA, ranging from 38% to 60% (Jordan et al., 2016, Lo-Ciganic et al., 2017), there is a paucity of information on the occurrence of adverse drug events (ADEs). The vast majority of patients with KOA are elderly, hence the occurrence of ADEs might be common. Age-related physiological changes, multiple comorbidities and polypharmacy are among the main contributors to the risk of ADEs (Dhalwani et al., 2017).

Falls are a major public health concern (Tinetti et al., 1988) and they are the leading cause of injury among people aged 65 years or over (Johnell et al., 2017). The use of medications (particularly those with CNS effects) has been identified as a risk factor for falls (Hanlon et al., 2017). The evidence on the association between analgesic use and the risk of fall was derived from systematic reviews and meta-analyses published since 1999. A systematic review by Leipzig et al. (1999) showed no significant association between the use of opioids and NSAIDs by older adults (aged 60 years or over) and the risk of fall. The reported pooled OR (95% CI) was 0.97 (0.78,1.20) and 1.16 (0.97,1.38) respectively (Leipzig et al., 1999). Subsequently, the results of a meta-analysis showed that the use of NSAIDs

was associated with an increased risk of falls, OR 1.21 (95% CI, 1.01,1.44), while no association was found between opioid use and the risk of falls, OR 0.96 (CI, 0.78,1.18) (Woolcott et al., 2009). More recently, Seppala et al. (2018), showed a significant association between falls and the use of opioids but not the use of NSAIDs, with pooled OR (95% CI) 1.60 (1.35, 1.91) for opioids and 1.09 (0.96, 1.23) for NSAIDs (Seppala et al., 2018a).

Unlike analgesics, the evidence on the association between antidepressant use and the risk of fall is more consistent. Leipzig et al. (1999) reported a significant association between antidepressant use and falls in older adults with pooled OR (95% CI) 1.66 (1.40, 1.95). These effects were independent of the participants' age, their frequency of falling and the study setting (community or long-term care). Subsequently, Woolcott et al. (2009) in their meta-analysis also reported an increased likelihood of falling with the use of antidepressants with adjusted pooled OR of 1.68 (95% CI, 1.47,1.91) (Woolcott et al., 2009). A similar association was found in a recent meta-analysis in which pooled OR (95% Cl) for any antidepressant was 1.57 (1.43,1.74) (Seppala et al., 2018b).

The association between AEDs and the risk of falls among community-dwelling patients is less studied; however, a significant association was reported between AED use and the risk of fall among those aged 60 years or more, OR 1.55 (95% CI 1.25, 1.92).(Seppala et al., 2018a).

Despite the existence of some evidence on the association between analgesic use (including antidepressants and AEDs), the above systematic

reviews included studies from various settings (such as inpatient wards and residential care facilities) (Seppala et al., 2018a). This implies that the studied population may not represent the population of patients with KOA in England, who are largely managed in the primary care setting. Additionally, the concomitant use of multiple analgesics by patients with OA generally and KOA specifically, has gained little previous attention. The impact of concomitant analgesics use on the risk of falls is not well described, although it has been shown that up to 53.9% of patients with OA use at least three drug regimens (Wilson et al., 2015). Hence, the association between analgesic use and the risk of fall in patients with KOA is not clear and there is a need to examine this association in detail.

It is essential that the burden of fall associated with the use of any as well as multiple analgesic classes in patients with KOA is quantified and understood. This will inform fall prevention planning and the provision of health and social care. The present study investigated the association between analgesic use and the risk for falls, within one year after KOA diagnosis.

7.2 Study Aim and Objectives

The overarching aim of the present study was to inform on the safety of analgesic use in patients with KOA. The study aim was to examine the association between the use of analgesics (antidepressants, AEDs, opioids,

NSAIDs and paracetamol) and the risk of fall in patients diagnosed with KOA in England. Specific study objectives were:

1. To estimate the risk of fall in patients using any analgesics within the first year of KOA diagnosis, compared to those not using any analgesics.
2. To estimate the risk of fall associated with the use of combined/multiple analgesic classes compared to no-analgesic use within the first year of KOA diagnosis

7.3 Methods

7.3.1 Study Design

This study used a cohort study design for a population that had primary care records in the CPRD with linkage to secondary care records from the Hospital Episode Statistics Admitted Patient Care data (HES APC).

7.3.2 Study Population

The patients included in this study were identified in the previous chapter (Chapter 6). These patients were diagnosed with KOA between 1st Jan 2000 and 31st Dec 2014 and had a record in the CPRD linked to HES data. Each patient's entry date was defined as the date of the first recorded diagnosis of KOA in CPRD and the patients were then followed up until the earliest of:

date of first fall, date of death, transfer out or end of follow-up period (December 31, 2015).

7.3.3 Exposure

The main exposure of interest was the prescription of analgesics; hence, patients with KOA were stratified into eight mutually exclusive exposure groups according to the analgesic drug classes prescribed during the first year after their KOA diagnosis (Table 7-1). The grouping was based on the clinical indication of the respective analgesic. For example, the NP medication group consisted of any use of antidepressants, AEDs or both. As reflected by its name, the drug classes included in this group are commonly used in clinical practice for the management of neuropathic pain (pain originating from nerve endings), either individually or simultaneously. The second analgesic group consisted of those who used opioids, whereas the third exposure group included patients who used non-opioid analgesics (NSAID, paracetamol). The remaining exposure groups consisted of combinations of these three single analgesic groups (Table 7-1).

Table 7-1 Treatment Groups According to the Prescribed Analgesics

Analgesic Treatment Groups	Description of Included Patients
No medication	Not prescribed any of the analgesics, hence do not belong to any of the above exposure groups, and form a group of no medications. This group will be the reference group for subsequent analyses of outcomes.
Neuropathic medication (NP) group	Prescribed antidepressants or anti-epileptic drugs or both
Opioid (OP) group	Prescribed opioids or opioids plus paracetamol (single tab/cap) or both
Non-opioid analgesics (ANA) group	Prescribed NSAIDs or plain paracetamol or both
NP+OP group	Prescribed any neuropathic medications and opioids, but not prescribed any non-opioid analgesics
NP+ANA group	Prescribed neuropathic medications and non-opioid analgesics, but not prescribed any opioids
OP+ANA group	Prescribed opioids (including opioid plus paracetamol in single tab/cap) and non-opioid analgesics, but not prescribed any neuropathic medications
NP+OP+ANA group	Prescribed all three analgesic groups: neuropathic medications, opioids and non-opioid analgesics

7.3.4 Outcome

The primary outcome was the first fall recorded within one year of KOA diagnosis. The definition of fall in the CPRD and HES was detailed in the previous chapter (Chapter 6). A fall was included only if it occurred after the date of the patient's entry into the study cohort and up to 31st December 2015. The date of occurrence of the fall used in the analysis was the first recorded date of fall during follow-up.

7.3.5 Study Covariates

The following baseline covariates were measured for each patient during the year prior to diagnosis:

1. Age: in years at the index diagnosis.
2. Gender: (male or female).
3. Deprivation score (as defined by the index of multiple deprivation (IMD) quintiles): this is an indicator based on area of residence and it covers 7 aspects of neighbourhood deprivation including income, employment, health deprivation and disability, education skills and training, barriers to housing and services, crime and living environment.
4. Previous fall (fall during the previous year): a previous fall within a year was consistently reported as a risk for a subsequent fall, hence the analysis controlled for it (Stubbs et al., 2015).
5. The use of other fall-risk-increasing drugs (FRIDs) was identified using corresponding CPRD ‘prod codes’. Information was extracted on FRIDs at baseline (1 year prior to the index diagnosis of KOA). This was to ensure the inclusion of the most up-to-date use of these medications, which in turn ensured the inclusion of all relevant medications that may affect the risk of falls. FRIDs include antipsychotics, benzodiazepines, hypnotics and antihypertensives.
6. Comorbidities as presented in chapters 5/6.

Information on all analgesic prescriptions generated during the follow-up period, along with information on fall events during the same period, was extracted.

7.3.6 Statistical Analysis

Two separate analyses were conducted; in the first analysis, exposure to analgesics during the first year after index diagnosis was defined as a **binary** variable and the risk of fall in analgesic users was compared to non-users. In the second analysis, exposure to analgesics was defined as a **categorical** variable and the risk of fall in patients using the different analgesic groups (described in Table 7-1) was compared to those not using any analgesics.

Cox's proportional hazards regression model was used to compare the risk of fall of analgesic users to that of non-users, and the risk of fall of the different treatment groups (exposure groups) compared to that of groups receiving no treatment. The results were reported as hazard ratio (HR) and 95% confidence interval (95% CI).

A separate multivariate Cox proportional hazards model was developed for each exposure definition (binary and categorical) where the HR and 95% CI were reported after adjusting for potential confounders listed under the study covariates. Age was tested as a continuous variable and as a categorical variable, with age at diagnosis being grouped into 4 ranks (<40, 40-64, 65-80,>80 years).

The strategy used for identifying confounding variables was:

1. Fit a model with the exposures of interest.
2. Conduct a univariate analysis: In the model of step 1, each potential confounder was added one at a time, in a sequential manner (one potential confounder was removed before the next was added). If a potential confounder changed the effect of the exposure by more or less than 10%, then this variable was considered in the fully adjusted model in step 3.
3. Fit the fully adjusted multivariate Cox proportional regression model using the variables from step 2 that were identified as confounders.

The steps carried out prior to running the main survival analysis are described in subsequent paragraphs. These steps included a graphical assessment of survivor function and statistical testing of the equality of survivor function, as well as the statistical testing of the proportional hazard's assumption.

7.3.6.1 Graphical Assessment of Survivor Function

Kaplan Meier (KM) curves were generated to estimate the occurrence of fall according to whether a patient was using any analgesics, and according to the analgesic treatment group.

7.3.6.2 Statistical Assessment of the Equality of Survivor Function

The log rank test was performed to check whether there were significant differences in the incidence of falls between patients using analgesics and those not using any over the first year after KOA diagnosis. The null hypothesis states that there is no difference in the survivor function between the two groups (those who used analgesics and those who did not use any) and between the groups using different analgesic treatments and those not using any analgesics.

7.3.6.3 Proportionality of Hazards Assumption Tests

The proportionality of hazards assumption was tested by Schoenfeld residuals (with significant p value, meaning that PH assumption is violated)

7.4 Results

7.4.1 Number and Proportion of Analgesic Users

The study included 57,383 patients, 44,010 (76.7%) of whom used analgesics within one year of KOA diagnosis and 13,373 (23.3%) of whom did not use any during the same period. A total of 21,222 (36.9%) patients used a single analgesic treatment group while 17,197 (29.9%) used dual and 5,591 (9.7%) used all three analgesic groups (Table 7-2). Of the 44,010 patients who used one or more analgesic treatment(s), the most common treatments were opioid and non-opioid analgesics (OP+ANA). These were used by 11,762 patients, representing 26.7% of total analgesic users (n=44,010), followed by the single treatment group of non-opioid analgesics (ANA), which were used by 11,112 patients, representing 25.2% of total analgesic users (Table 7-2).

Table 7-2 Number (%) of Patients per Analgesic Treatment Group

Analgesic Treatment	**Analgesic Group**		**Number of Users N=57,383 (% from total population)**
None			13,373 (23.5)
Single treatment	Neuropathic analgesics	NP	1,954 (3.4)
	Opioid analgesics	OP	8,156 (14.2)
	Non-opioid analgesics	ANA	11,112 (19.3)
Total single treatment users			**21,222 (36.9)**
Dual treatment	Neuropathic analgesics & opioid analgesics	NP+OP	3,165 (5.5)
	Neuropathic analgesics & non-opioid analgesics	NP+ANA	2,270 (3.9)
	Opioid analgesics & non-opioid analgesics	OP+ANA	11,762 (20.5)
Total dual treatment users			**17,197 (29.9)**
Total all three treatment users	Neuropathic analgesics & opioid analgesics & non-opioid analgesics	NP+OP+ ANA	**5,591 (9.7)**

7.4.2 Sociodemographic and Clinical Characteristics of the Study Population

The sociodemographic and clinical characteristics of the study population are presented in Table 7-3. Patients who were prescribed analgesics were older than those who were not prescribed any analgesics: mean age 68.1 (SD12.55) years and 63.5 (SD13.08) years respectively. Analgesic users constituted the majority (59.9%) within the older age group (aged 65 years and over) while non-users formed the majority (54.6%) of the younger age groups (aged less than 40 years and 40–64 years) (Figure 7-1).

Analgesic users' were more likely to be females [(62.4% (n= 27,442)] compared to 49.3% (n=6,584) of the non-users' group.

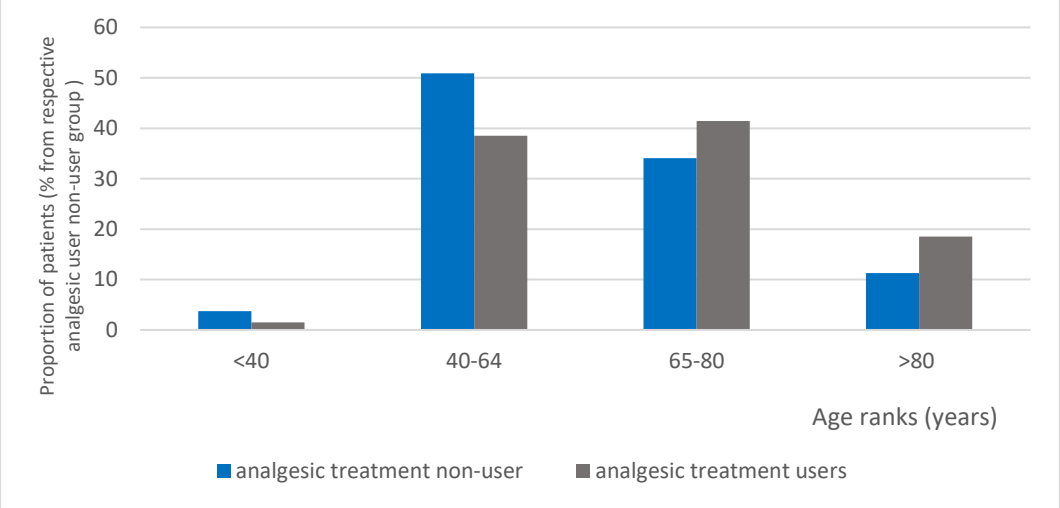


Figure 7-1 Proportion of Treatments Users and Non-users by Age Group

Table 7-3 Demographic, Socioeconomic and Clinical Characteristics of Analgesic Users and Non-users

	Overall study population	**Any analgesic**	
		Users	Non-users
Number of patients (% from respective analgesic user/non-user)	57,383	44,010 (100)	13,373 (100)
Gender			
Male	23,357	16,568 (37.6)	6,789 (50.7)
Female	34,026	27,442 (62.4)	6,584 (49.3)
Mean age (SD) years (Range)	67.0 (12.82) (18.0–104.7)	68.1 (12.55) (18.3–104.7)	63.5 (13.08) (18.0–104.5)
Age group			
<40 years	1,157	656 (1.5)	501 (3.7)
40-64 years	23,773	16,963 (38.5)	6,810 (50.9)
65-80 years	22,787	18,236 (41.5)	4,551 (34.0)
>80 years	9,666	8,155 (18.5)	1,511 (11.4)
IMD score*			
1	12,106	8,502 (19.3)	3,604 (26.9)
2	13,423	10,048 (22.5)	3,375 (25.3)
3	12,151	9,339 (21.2)	2,812 (21.0)
4	11,061	8,830 (20.1)	2,231 (16.7)
5	8,619	7,274 (16.5)	1,345 (10.1)
Missing	23	17 (0.004)	6 (0.003)
Comorbidity	9,492	8,102 (18.4)	1,390 (10.4)
FRID	33,276	27,275 (61.9)	6,001 (44.8)
Previous fall	4,852	4,087 (9.3)	765 (5.7)

*Data available for 57,360 patients. SD standard deviation; IMD index of multiple deprivation; FRID fall risk increasing drugs

Within analgesic users, a total of 18,550 (42.2%) were within the least deprived IMD category, while 16,104 (36.6%) were in the most deprived category. With regard to non-users of analgesics, 6,979 (52.1%) of the non-users were in the least deprived category, compared to 26.8% in the most deprived (Table 7-3).

More than two-thirds of analgesic users (61.9%) were prescribed one or more other FRIDs (n=27,275) while just half (49.9%) of analgesic non-users were prescribed other FRIDs (n= 6,001). Within the analgesic users' group, 8,102 patients (18.4%) had at least one comorbidity at baseline, compared to 1,390 patients (10.4%) of analgesic non-users. Of analgesic users, 4,087 (9.3%) had a previous fall compared to 765 (5.7%) non-users (Table 7-3).

The sociodemographic and clinical characteristics of patients with KOA prescribed different analgesics are summarised in Table 7-4. Females constituted the majority among analgesic users and across treatment groups (Figures 7-2 and 7-3). Of particular note is the group of all three analgesics, in which females constituted 74.4%, (n=4,164) followed by the NP+OP and NP+ANA groups, where females constituted 70.5% (n= 2,233) and 70.2% (n=1,592) of total patients respectively group (Figure 7-6).

Patients in the (OP+ANA) and (NP +ANA) treatment groups were older than those in the other treatment group: mean age 69.17 (SD ±11.86) years and 68.78 (SD±13.66) years, respectively (Table 7-4).

At least one comorbidity was recorded at baseline in 8,102 patients (30.60%) of all three analgesic treatments groups and in 695 patients

(30.60%) of the (NP+ANA) treatment users. However, only 1,362 patients (12.30%) of those using non-opioid analgesics (ANA) had a record of comorbidity at baseline (Table 7-4).

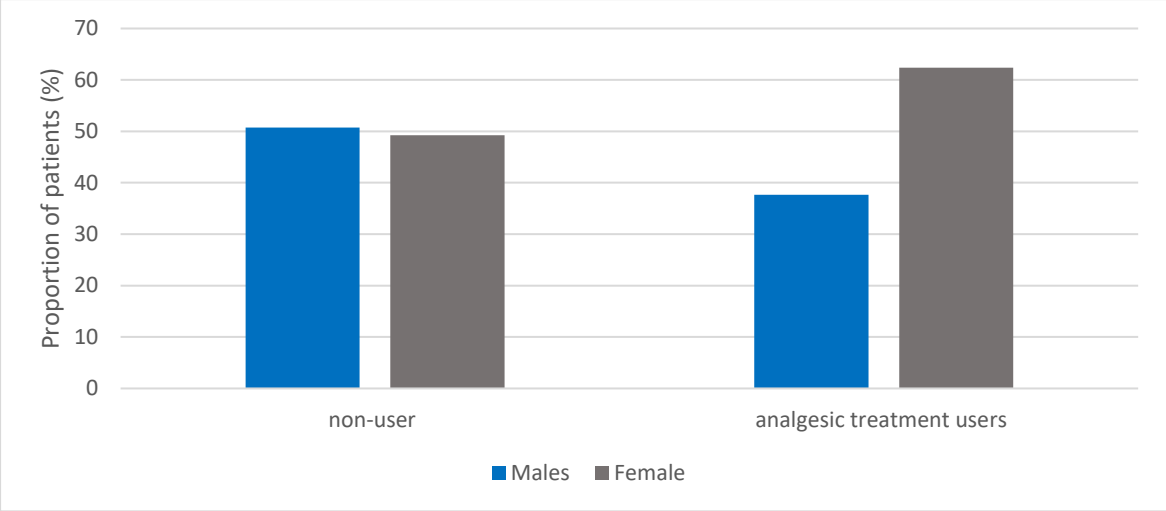
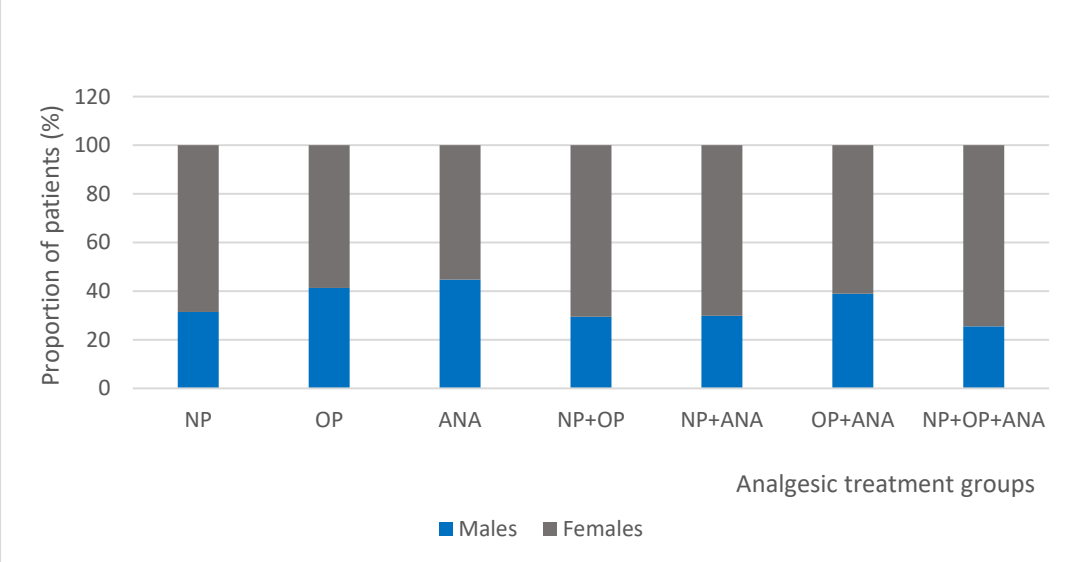


Figure 7-2 Proportion of Analgesic Users and Non-users by Gender



NP neuropathic pain analgesics; OP opioid analgesics; ANA non-opioid analgesics

Figure 7-3 Gender Distribution by Analgesic Treatment Groups

Table 7-4 Characteristics of Patients with KOA Using Different Analgesics

No. of Patients (% from Total in Respective Treatment Group)								
	NP	**OP**	**ANA**	**NP+ OP**	**NP+ ANA**	**OP+ ANA**	**NP + OP+ ANA**	**Total users**
		8,158	11,112	3,165	2,270	11,763	5,593	44,010
Gender								
Male	615 (31.5)	3,374 (41.3)	4,963 (44.7)	932 (29.5)	678 (29.8)	4,579 (38.9)	1,429 (25.5)	16,570 (37.7)
Female	1,339 (68.5)	4,784 (58.7)	6,149 (55.3)	2,233 (70.5)	1,592 (70.2)	7,184 (61.1)	4,164 (74.4)	27,445 (62.3)
Mean age years (SD)	63.32 (13.26	68.32 (12.23)	68.67 (12.58)	66.09 (12.87)	68.78 (13.66)	69.17 (11.86)	66.83 (12.83)	-
Age group (years)								
<40	70 (3.6)	110 (1.3)	173 (1.5)	40 (1.2)	50 (2.2)	121 (1.0)	92 (1.6)	656 (1.5)
40–64	1,024 (52.4)	3,039 (37.2)	4,075 (36.6)	1,480 (46.7)	847 (37.3)	4,063 (34.5)	2,435 (43.5)	16,963 (38.5)
65–80	622 (31.8)	3,531 (43.3)	4,655 (41.9)	1,129 (35.6)	853 (37.6)	5,344 (45.4)	2,105 (37.6)	18,239 (41.4)
>80	238 (12.2)	1,478 (18.1)	2,209 (19.9)	516 (16.3)	520 (22.9)	2,235 (19.0)	961 (17.2)	8,157 (18.5)
IMD score								
1	469 (24.0)	1,574 (19.3)	2,436 (21.9)	544 (17.2)	423 (18.6)	2,165 (18.4)	892 (15.9)	8,503 (19.3)
2	485 (24.8)	1,918 (23.5)	2,681 (24.1)	674 (21.3)	530 (23.3)	2,652 (22.5)	1,109 (19.8)	10,049 (22.8)
3	392 (20.1)	1,688 (20.7)	2,497 (22.5)	635 (20.1)	517 (22.8)	2,462 (20.9)	1,150 (20.6)	9,341 (21.2)
4	381 (19.5)	1,625 (19.9)	2,099 (18.9)	664 (20.9)	429 (18.9)	2,401 (20.4)	1,232 (22.0)	8,831 (20.0)
5	226 (11.5)	1,351 (16.5)	1,397 (12.5)	646 (20.4)	371 (16.3)	2,079 (17.6)	1,204 (21.5)	7,274 (16.5)
Comor bidity	557 (28.5)	1,264 (15.5)	1,362 (12.3)	931 (29.4)	695 (30.6)	1,735 (14.7)	1,558 (27.8)	8,102 (30.6)
FRID use	1,082 (55.3)	5,129 (62.8)	5,886 (52.9)	2,228 (70.4)	1,509 (66.5)	7,480 (63.6)	3,961 (70.8)	27,275 (61.9)
Previo- us fall	180 (9.2)	700 (8.6)	812 (7.3)	389 (12.3)	281 (12.4)	994 (8.4)	731 (13.1)	4,087 (9.3)

NP neuropathic pain analgesics; OP opioid analgesics; ANA non-opioid analgesics; SD standard deviation; IMD index of multiple deprivation; FRID fall risk increasing drugs

7.4.3 Number and Proportion of Patients who had Experienced a Fall

Within one year of KOA diagnosis, 2,384 patients experienced a fall (4.1% of the total HES-linked population n=57,383). A total of 9 patients had a fall on the day of index diagnosis of KOA and were excluded in further analyses, leaving a total of 57,374 patients, with 2,375 patients who had a recorded fall within one year of KOA diagnosis (Table 7-5).

Table 7-5 Number (%) of Patients who Experienced a Fall by any Analgesic Use

	Analgesic User	**Non-User**	**P Value**
Total	44,010 (100%)	13,364(100%)	
Patients who experienced a fall	2,125 (4.8%)	250 (1.8%)	<0.001
Patients who did not experience a fall	41,885 (95.2%)	13,114 (98.2%)	<0.001

The number and proportions of patients who experienced a fall, by analgesic treatment groups, are presented in Table 7-6. Across analgesic treatment groups, the proportion of patients with a recorded fall within one year of KOA diagnosis ranged from 3.2% in the neuropathic medication users (NP) up to 29.0% in the opioid and non-opioid (OP+ANA) users. Nearly a third (n=615, 29.0%) of all falls were experienced by those who used both opioids and non-opioid analgesics (OP+ANA), while 21.3% (n=453) of all falls were experienced by those using all three analgesic classes (NP+OP+ANA) within one year after KOA diagnosis.

Table 7-6 Number (%) of Patients who Experienced a Fall by Analgesic Treatment

Analgesic Treatment	Analgesic Treatment	Analgesic Classes	Number of Patients who Experienced a Fall (% from Total n=2,125)
Single	Neuropathic analgesics	NP	68 (3.2%)
	Opioid analgesics	OP	283 (13.4%)
	Non-opioid analgesics	ANA	381 (17.9%)
Dual	Neuropathic analgesics and opioid analgesics	NP+OP	175 (8.2%)
	Neuropathic analgesics and non-opioid analgesics	NP+ANA	150 (7.0%)
	Opioid analgesics and non-opioid analgesics	OP+ANA	615 (29.0%)
All Three	Neuropathic analgesics and opioid analgesics and non-opioid analgesics	NP+OP+ANA	453 (21.3%)

7.4.4 Cox Proportional Regression with Analgesic use Defined as a Binary Variable

The results of the two steps carried out prior to running the main survival analysis are presented first. These steps included a graphical assessment of survivor function and statistical testing of the equality of survivor function. These are followed by the results on the association between each analgesic treatment group and the risk of fall, reported as HR (95% CI).

7.4.4.1 Graphical Assessment of Survivor Function

The KM curve for survivor functions were generated (Figure 7-4). These plots showed that the risk of fall was higher in analgesic users compared to non-users. A clearer version of the KM graph is included in Appendix 8.

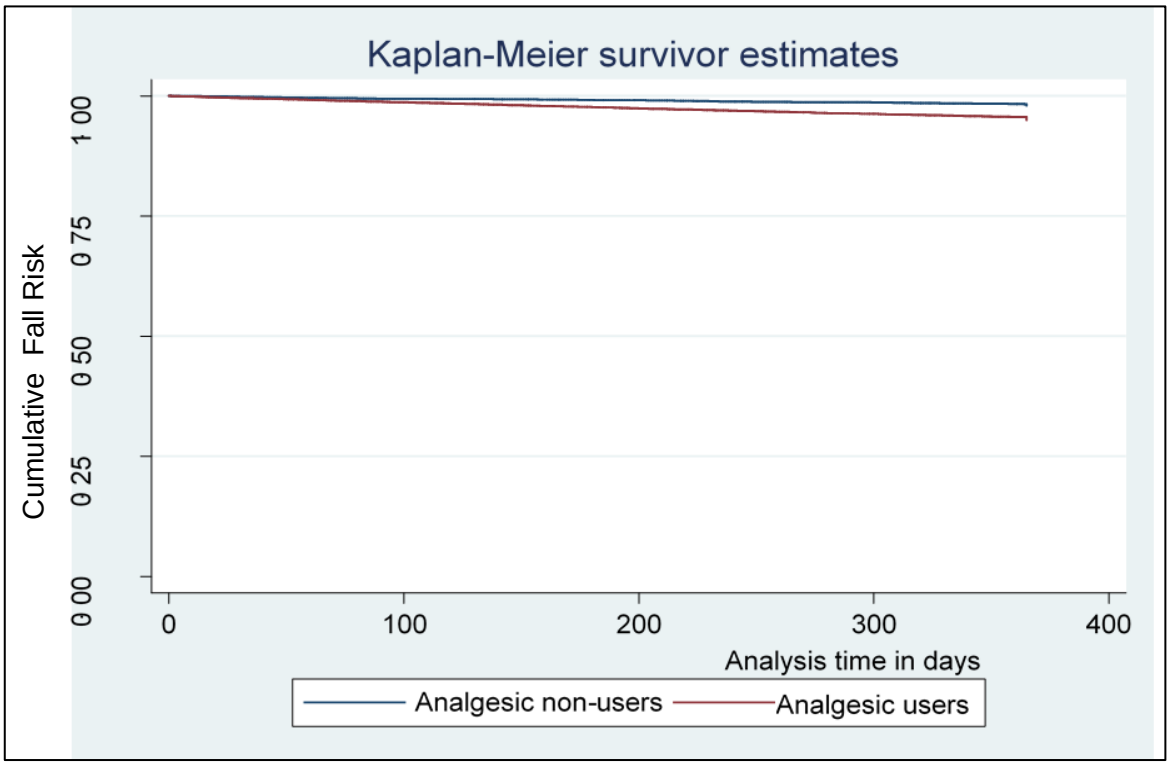


Figure 7-4 Kaplan Meier Survival Estimates for Analgesic Users and Non-users

7.4.4.2 Statistical Assessment of the Equality of Survivor Function

The results of the log rank test for the statistical assessment of equality of survival function are presented in Table 7-7. The p-value was <0.001, which means that there was a statistically significant difference in survival (occurrence of fall) between analgesic users and non-users (null hypothesis must be rejected).

Table 7-7 Log-rank Test for Equality of Survivor Function

Use of any Analgesic	Observed Events	Expected Events
No	250	550.19
Yes	2,125	1,824.81
Total	2,375	2,375.00

7.4.4.3 Cox Proportional Hazards Regression with Analgesic Exposure Defined as a Binary Variable

The unadjusted hazard ratio for the use of any analgesic was 2.57 (95% CI 2.24, 2.91). The p-value here was from a Wald significance test ($p < 0.001$) This meant that the hazard rate of fall in patients using analgesics was 2.57 times the hazard rate in patients not using any analgesics, with 95% confidence that the true hazard ratio was between 2.24 and 2.91. Hence, there was a significant association between using analgesics and the hazard of fall in patients with KOA.

7.4.4.4 Proportionality of Hazards Assumption

The proportionality of hazards assumption was checked statistically.

The global test for the proportional hazard assumption (chi^2 0.88) was not statistically significant. (p-value 0.3480). Hence, there is no evidence to reject the assumption for proportional hazards for use of analgesics.

7.4.4.5 Effect of Confounders on the Risk for Fall (Univariate Analysis)

When each potential confounder was added to the Cox regression model separately and sequentially one at a time, a change in the hazard ratio was observed, as seen in Table 7-8. The resulting change in HR varied with different confounders; however, age, gender and use of FRIDs appeared to have a significant effect (±10% change of the HR) and they were therefore included in the final fully adjusted model.

Table 7-8 Results of the Univariate Analysis

Potential Confounder	Reference Group	HR (95% CI)	P-Value
Age at index diagnosis of KOA	Younger age	1.98 (1.73, 2.26)	<0.001
Age group	<40 years	2.07 (1.81, 2.36)	<0.001
Gender	Males	2.39 (2.09, 2.72)	<0.001
IMD score	least deprived	2.56 (2.25, 2.92)	<0.001
FRID use	No use of FRIDs	2.29 (2.00, 2.61)	<0.001
Comorbidity	No comorbidity	2.48 (2.18, 2.84)	<0.001
Previous fall	No previous fall	2.50 (2.19, 2.85)	<0.001

IMD index of multiple deprivation; FRID fall risk increasing drugs; HR Hazard ratio; CI confidence interval

7.4.4.6 The Final Model

The results of the adjusted HR (95% CI) for fall with each covariate as well as the p-value are presented in Table (7-9).

Table 7-9 Covariates Adjusted for the Final Cox Regression Model

	HRadjusted	95% CI	P-Value
Analgesic use	1.89	1.66, 2.16	< 0.0001
Age group (years)			
40–64	1.68	0.90, 3.16	0.102
65–80	3.27	1.75, 6.12	< 0.001
>80	9.48	5.07, 7.72	< 0.001
Gender (male)	1.57	1.43, 1.72	< 0.001
Use of FRIDs (no FRIDs use)	1.42	1.29, 1.56	< 0.001

FRID fall risk increasing drugs; HR hazard ratio; CI confidence interval

The HRs for fall according to analgesic use, both unadjusted and adjusted for potential confounding variables, are summarised in Table 7-10. The results showed that compared to non-users, patients using analgesics were

exposed to 89% greater risk of fall, after controlling for age at diagnosis (as a categorical variable), gender and prescription of FRIDs. The p-value is still statistically significant, indicating a significant association between the use of analgesics and the hazard rate.

Table 7-10 Hazard Ratios for Fall by Analgesic Use

Analgesic Use Status	**HR (95%CI)**	**P-Value**	**HR adjusted* (95%CI)**	**P-Value**
Not used	1	-	1	-
Used	2.57 (2.24, 2.91)	< 0.001	1.89 (1.66, 2.16)	< 0.001

*Adjusted for age, gender and prescription of FRIDs. HR hazard ratio; CI confidence interval

7.4.5 Cox Proportional Regression with Analgesic Use Defined as a Categorical Variable

In this subsection, analgesic use was defined as a categorical variable (as opposed to a binary variable in the previous subsection). The steps carried out prior to running the main survival analysis are presented first. These steps included a graphical assessment of survivor function and statistical testing of the equality of survivor function. Results on the association between the use of each analgesic treatment group and the risk of fall are reported as HR (95% CI).

7.4.5.1 Graphical Assessment of Survivor Function

The KM curve for survival functions were plotted (Figure 7-5) and these graphs showed that the risk of fall was lower in the non-user group compared to the risk with the use of any of the different analgesic treatments. A clearer version of the graph is included in Appendix 8.

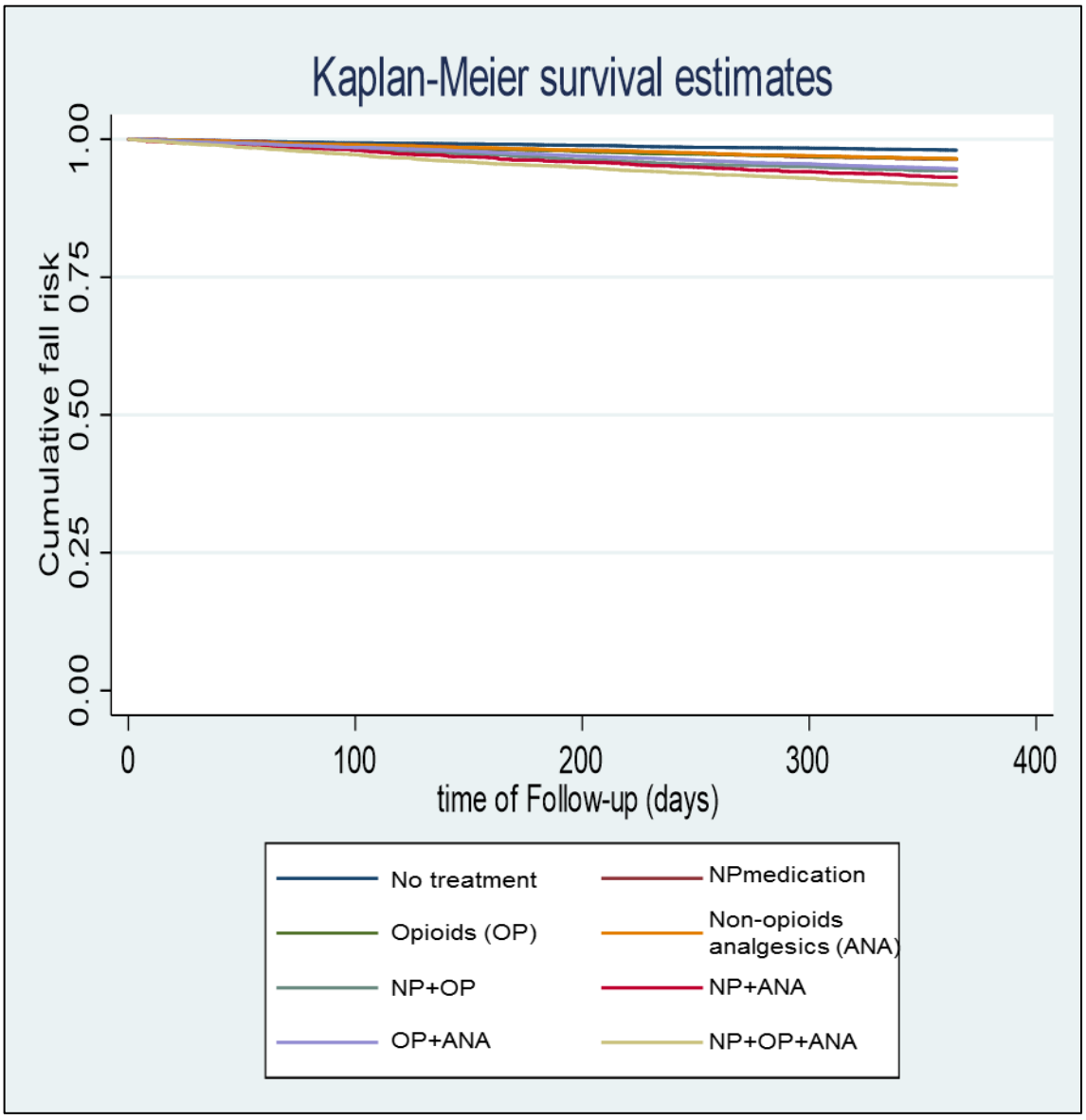


Figure 7-5 Survival Function for the Different Analgesic Treatment Groups

7.4.5.2 Statistical Testing of Equality of Survivor Functions

The results of the log rank test performed and showed that there was a statistically significant difference in survival (occurrence of fall) between the different analgesic treatment users and analgesic non-users.

7.4.5.3 Cox Proportional Hazards Regression with Analgesic Use Defined as a Categorical Variable

The unadjusted HR (95% CI are presented in Table 7-11. The results show that compared to patients not using any analgesics, those using all analgesic groups are at a greater risk of falls. The risk varied according to the number and type of analgesics used.

Table 7-11 Risk of Fall According to Analgesic Treatment Group

Analgesic Treatment Group		**HR (Unadjusted)**	**95% CI**	**P-Value**
	No treatment	Reference	-	-
Single Treatment groups	NP	1.86	1.42, 2.43	<0.001
	OP	1.85	1.56, 2.19	<0.001
	ANA	1.81	1.54, 2.12	<0.001
Dual Treatment Groups	NP+OP	2.98	2.46, 3.62	<0.001
	NP+ANA	3.60	2.94, 4.41	<0.001
	OP+ANA	2.76	2.38, 3.20	<0.001
Three Treatment Groups	NP+OP+ANA	4.37	3.74, 5.10	<0.001

NP neuropathic pain analgesics; OP opioid analgesics; ANA non-opioid analgesics; HR hazard ratio; CI confidence interval

The results of the HR for fall indicate that compared to patients who are not using any analgesics, those who are using a single analgesic treatment group i.e. neuropathic pain medicines (NP), opioid analgesics (OP) or non-opioid analgesics (ANA) are at a greater risk of fall. The HRs (95% CI) were 1.86 (1.42, 2.43), 1.85 (1.56, 2.19) and 1.81 (1.54, 2.12), respectively.

Patients using dual analgesic treatment groups, i.e. neuropathic pain medicines and opioids (NP+OP) or neuropathic medicines and non-opioid analgesics (NP+ANA) or opioids with non-opioid analgesics (OP+ANA) were also at a greater risk of fall compared to patients not using any analgesics. The HRs (95% CI) were 2.98 (2.46, 3.62), 3.60 (2.94, 4.41) and 2.76 (2.38, 3.20) respectively.

Patients with KOA who used all three analgesic treatment groups within one year of KOA diagnosis had 4.37 times a greater risk of fall than those who did not use any analgesics over the same period.

7.4.5.4 Proportionality of Hazards Assumption

The proportionality of hazards assumption was tested statistically and was found not to be statistically significant (p-value =0.25); hence, there is no evidence to reject the assumption for proportional hazards for the use of analgesics.

7.4.5.5 Effect of Confounders on the Risk of Fall (Univariate Analysis)

When each potential confounder was added to the Cox regression model separately and sequentially, one at a time as described in the methods section of this chapter, a change in the hazard ratio was observed as seen in Table 7-12. The resulting change in HR varied with different confounders; however, age, gender and use of FRIDs appeared to have a significant effect (>10 % change of the HR) based on their effect on the (NP+OP) treatment group. These were therefore included in the final fully adjusted model.

Table 7-12 Observed Changes in HR by Analgesic Group when each Covariate was Included Separately in the Model

Analgesic Treatment Group	Unadjusted	Age	Age Group	Gender	Comorbidity	FRIDs Use	Previous Fall	IMD Score
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
No analgesics	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
NP	1.86	1.89 (1.44–2.47)	1.86 (1.42–2.43)	1.68 (1.29–2.20)	1.76 . (1.34–2.30)	1.74 (1.33–2.28)	1.82 (1.39–2.38)	1.87 (1.43–2.45)
OP	1.85	1.42 (1.20–1.69)	1.47 (1.24–1.75)	1.76 (1.48–2.09)	1.82 . (1.53–2.16)	1.65 (1.39–1.95)	1.81 . (1.53–2.15)	1.87 . (1.57–2.21)
ANA	1.81	1.34 (1.14–1.57)	1.41 (1.20–1.65)	1.75 (1.49–2.06)	1.80 (1.53–2.11)	1.72 (1.46–2.01)	1.79 (1.53–2.10)	1.81 (1.55–2.13)
NP+OP	2.98	2.53 (2.08–3.07)	2.58 (2.13–3.13)	2.68 (2.20–3.25)	2.81 . (2.31–3.41)	2.54 (2.09–3.09)	2.85 (2.35–3.46)	3.03 . (2.49–3.68
NP+ANA	3.60	2.57 (2.09–3.15)	2.72 (2.22–3.33)	3.24 (2.64–3.97)	3.38 (2.76–4.14)	3.15 . (2.57–3.86)	3.45 (2.81–4.22)	3.63 . (2.96–4.45)
OP+ANA	2.76	2.03 (1.75–2.35)	2.14 (1.85–2.48)	2.60 (2.24–3.01)	2.72 (2.35–3.16)	2.45 (2.11–2.84)	2.71 (2.34-3.14)	2.79 (2.41-3.24)
NP+OP+ANA	4.37	3.61 (3.09– 4.21)	3.72 (3.18– 4.34)	3.86 (3.30–4.51)	4.14 (3.54–4.84)	3.72 (3.19–4.35)	4.16 (3.56-4.86)	4.44 (3.80-5.18)

NP neuropathic pain analgesics; OP opioid analgesics; ANA non-opioid analgesics; IMD index of multiple deprivation; FRID fall risk increasing drugs; HR hazard ratio; CI confidence interval

7.4.5.6 Final Adjusted Model

The results of the final adjusted model showed that compared to non-users, patients using different groups of analgesics were at a higher risk of falling, after controlling for age at index diagnosis, gender and prescription of FRIDs. The risk of fall varied according to the analgesic treatment group used. The HR (95% CI) ranged from 1.36 (1.16–1.60) with the non-opioid analgesic group (ANA) to 3.24 (2.773.78) with the use of all three analgesic groups (NP+OP+ANA). In Table 7-13, the HRs for fall according to analgesic treatment group, both unadjusted and adjusted for the potential confounding variables, are summarised.

The risk of fall associated with analgesics use increased in proportion to the number of analgesic treatments. The HR (95% CI) associated with the use of all three analgesic treatment groups was greater than that associated with the use of dual analgesic treatment groups (3.24 (2.77, 3.78) vs 2.28 (1.87, 2.77), 2.45 (1.99, 3.00) and 1.99 (1.71, 2.31)). The HRs (96% CI) associated with the use of dual analgesic treatment groups were in turn greater than the risk with the use of a single analgesic treatment group: HR (95% CI) 1.70 (1.30, 2.23), 1.38 (1.16, 1.64) and 1.36 (1.16, 1.60) for NP, OP and ANA respectively (Table 7-13).

The adjusted HR is highest with the use of all three analgesic groups; patients using all three analgesic groups were exposed to a risk of fall 3 times greater than those not using any analgesics: HR (95% CI) 3.24 (2.77, 3.78). Patients using neuropathic pain medication with opioids or non-opioid analgesics had from twice up to 3.5 times the risk of fall compared to those

not using any analgesics: HR (95% CI) 2.28 (1.87, 2.77) and 2.45 (1.99, 3.00) respectively.

Table 7-13 Risk of fall by analgesic use, unadjusted and adjusted for confounders

	Unadjusted		**Adjusted***	
Analgesics	HR (95% CI)	p-values	HR (95% CI)	p-values
No use	1.0	Reference	1.0	Reference
NP	1.86 (1.42, 2.43)	< 0.001	1.70 (1.30, 2.23)	< 0.001
OP	1.85 (1.56–2.19)	< 0.001	1.38 (1.16, 1.64)	< 0.001
ANA	1.81 (1.54–2.12)	< 0.001	1.36 (1.16, 1.60)	< 0.001
NP+OP	2.98 (2.46–3.62)	< 0.001	2.28 (1.87, 2.77)	< 0.001
NP+ANA	3.60 (2.94, 4.41)	< 0.001	2.45 (1.99, 3.00)	< 0.001
OP+ANA	2.76 (2.38–3.20)	< 0.001	1.99 (1.71,2.31)	< 0.001
NP+OP+ANA	4.37 (3.74,5.10)	< 0.001	3.24 (2.77, 3.78)	< 0.001

* Adjusted for age, gender and prescription of FRIDs. NP neuropathic pain analgesics; OP opioid analgesics; ANA non-opioid analgesics; FRID fall risk increasing drugs; HR hazard ratio; CI confidence interval

7.5 Discussion

7.5.1 Main Findings

In this population-based cohort of patients with KOA, the prevalence of analgesic use was found to be 76.7% during the first year after KOA diagnosis. Analgesic users were at 1.89 times the risk of falls compared to non-users (HR 1.89, 95% CI 1.66, 2.16) after adjusting for age, gender and the use of other FRIDs.

To study the association between analgesic use and the risk of fall, eight different analgesic exposure groups were constructed based on the type and number of analgesic classes used by each patient during the first year after diagnosis. These exposure groups included single, dual or triple analgesic treatment groups.

The risk of fall associated with the use of each of the treatment groups was compared to the risk in non-users, during the first year after KOA diagnosis. The results showed that the risk of fall varied according to the number and types of analgesic classes used; the risk of fall was highest in patients using all three analgesic groups (NP+OP+ANA) with a risk more than three times that of not using any analgesics over the same time period (HR 3.24, 95%CI 2.77, 3.78) after controlling for age, gender and the use of other FRIDs.

7.5.2 Comparison with Current Literature

7.5.2.1 Prevalence of Analgesics Prescriptions

The prevalence of analgesic use was found to be 76.7%, which is higher than that reported in other studies on analgesic prescribing in patients with musculoskeletal conditions or OA (Muller et al., 2012, Knoop et al., 2017, Lo-Ciganic et al., 2017).

Analgesic prescribing in primary care patients with non-inflammatory musculoskeletal (MSK) pain was investigated by Muller et al. (2012*)* in a study that aimed to describe analgesic prescribing using a regional primary care database. The authors reported that 62% of UK primary care patients with MSK conditions (n=428, mean age 65 years [SD10]) were prescribed an analgesic at their first consultation in primary care (Muller et al., 2012). The widespread use of analgesics in patients with OA was also reported in a cross-sectional study including 656 patients with knee and/or hip OA referred to an outpatient centre in Amsterdam. Analgesic use was self-reported, and the patients were asked to list all the analgesics they used. The results showed that 63% (n=412) of the study population used analgesics, while 37% (n=153) did not use any (Knoop et al., 2017).

In a recent prospective study of 4,231 participants aged 45–79 years at baseline who were diagnosed with OA and followed up for 4 years, 60% used at least one analgesic or nutraceutical agent (e.g. chondroitin) for their pain during follow-up (Lo-Ciganic et al., 2017). Using CPRD data, the prevalence of analgesic prescribing among patients with incident OA was

34.7% in 2013 (n=25,245), calculated based on prescriptions issued within 14 days of incident OA consultation (Yu et al., 2017).

The higher proportion of analgesic users in the present study's cohort of patients with KOA compared to those reported in previous studies could possibly be explained by the inclusion of antidepressants and AEDs in the present study, in addition to the analgesics included in the studies by Muller and Knoop (opioid, paracetamol and NSAIDs). The study by Yu using CPRD data measured the prevalence of opioids and NSAIDs but not paracetamol, hence there was a lower percentage of users compared to the present study.

In contrast to the younger patients who frequently used non-opioid analgesics (ANA), the most frequently used analgesic treatment group in those aged 65 years and over was OP+ANA. The use of opioids in older age groups was also reported in a previous UK-based study (Ruscitto et al., 2015). In 2015, Ruscitto et al. conducted a geographically-defined study using patient-level population data of dispensed analgesics to examine the proportion of adults in Scotland who were dispensed opioids between 1995 and 2010. The study included 311,881 patients registered at an NHS Tayside GP in 2010 and it reported that 7.8% of patients in the very old age group (85 years and older) received strong opioids compared to 4% in the 45-to-64- year-old group and 6.6% in the 65-to-84-year-old group.

7.5.2.2 Risk of Fall in Different Treatment Groups

Comparison with other studies that have investigated the association between medication use and the risk of fall might be challenging. Unlike other studies focussing on the risk of fall associated with the use of a single/specific analgesic class (e.g. opioids or antidepressants), the current study included exposure to a range of analgesics, including five different classes grouped into seven different treatment groups.

The present study found that the use of any analgesic within a year after KOA diagnosis was associated with an 89% higher risk of fall compared to the risk of those not using any analgesics over the same period. Furthermore, the risk varied across the seven treatment groups that were constructed to represent the actual (real-life) drug exposure in patients with KOA.

The risk associated with NP medications' use was consistent with findings from previous studies on antidepressants and AEDs. For example, the use of antidepressants was associated with an increased risk of recurrent falls in a longitudinal analysis of 4,231 patients with OA, RRadjusted 1.25 (95% CI 1.10, 1.41) (Lo-Ciganic et al., 2017). In the study by Lo-Ciganic et al. (2017), opioid use was associated with an increased risk of recurrent falls RRadjusted 1.22 (95% CI 1.04, 1.45), adjusted for several important confounders. In a separate study among community-dwelling adults aged 60 years or over, opioid use was associated with an increased risk of fall OR (95% CI) 2.4 (1.5, 3.7) (Masud et al., 2013). Additionally, in a population-based nested case control study, using data from the region of Scania's

healthcare database, the risk of fall associated with opioid use was reported separately for men and women as follows: OR (95% CI) 1.92 (1.68, 2.20) and 1.90 (1.49, 2.24) respectively (Modén et al., 2010).

The findings from the present study on the association of non-opioid analgesics and the risk of fall were in line with those reported in a cross-sectional study among 4,000 community-dwelling adults aged 65 years or over. The risk was reported as OR (95% CI) 1.46 (1.03, 2.07) for NSAIDs and 1.62 (1.0, 2.64) for paracetamol (Lee et al., 2006). However, the present study's findings were contrary to those reported in several other studies that have failed to demonstrate any significant association between exposure to NSAIDs and the risk of fall in community-dwelling adults. The reported ORs (95% CI) from those studies were 1.25 (0.24, 6.5), 1.02 (0.78, 1.32), 1.41 (0.98, 2.04) and 1.26 (0.93, 1.71) (Toulotte et al., 2006, Hanlon et al., 2002, Lee et al., 2006, Ham et al., 2014) respectively. Unlike the present study, these previous studies were limited by the small sample size (n=40) (Toulotte et al., 2006) and inadequate control of confounding factors, i.e. adjusted for age and gender only (Lee et al., 2006), or a fall was recorded at yearly intervals (i.e. a fall during the past year was recorded during a yearly interview for 3 years). This constitutes a potential source of recall bias, possibly resulting in an underestimation of the incidence of falls (Hanlon et al., 2002). In the study by Ham et al., (2014) half of the participants were prescribed vitamin B and folic acid supplements and all of the participants were prescribed vitamin D supplements (n=2,407) during the follow-up period of 2–3 years (Ham et al., 2014). This may have resulted

in an underestimation of fall risk in the studied sample as some evidence suggests that vitamin D supplements may reduce the risk of fall in people with low vitamin D levels (Gillespie et al., 2012).

Additionally, the estimates reported in the present study were higher than those reported by some previous studies (Lo-Ciganic et al., 2017). This could be explained by the fact that the ascertainment of falls was through self-reporting during regular interviews conducted at fixed intervals. For example, in Lo-Ciganic's work, the interviews were conducted at the end of each year when patients were asked about the occurrence of falls during the past year. Medication use during the month preceding the date of the annual interview visit was also self-reported. The self-reported fall data may have introduced a recall bias, which could have led to an underestimation of the real prevalence of falls (Ganz et al., 2005).

The impact of multiple CNS medication use was studied among community-dwelling adults who enrolled in a Health and Body Composition (Health ABC) study between 1997 and 1998 (Hanlon et al., 2009). The study included 3,055 participants with a mean age of 74 (SD 2.87) years. The use of multiple medications increased the risk of recurrent falls compared to no use ORadjusted 1.95 (95% CI 1.35, 2.81). CNS medication included opioids, antidepressants, antipsychotics and benzodiazepines. The findings from the present study were in line with those reported by Hanlon et al. (2009); however, the present study found a stronger association between the use of all three drug classes and the risk of fall: HR 3.24 (95% CI 2.77, 3.78) adjusted for age, sex and the use of other FRIDs.

7.5.3 Strengths and Limitations

The key strength of the present study was that it investigated the association between the use of a range of analgesics recommended by clinical guidelines (NICE, 2014, OARSI, 2014) and commonly used in clinical practice for the management of KOA-related pain and the risk of fall in patients with KOA. It also estimated the risk of falls in patients who used multiple analgesic treatments and provided detailed information on the prevalence of use of each analgesic treatment group, using a population-based sample. Also, patients who used AEDs and antidepressants were included.

In the present study, the methods for ascertaining medication use and falls were extracted from the CPRD and HES databases; medication use was based on prescriptions using specific product codes, while falls were identified by relevant Read and ICD-10 codes. This ensured the validity and completeness of analgesic exposure and data on fall events, and avoided any potential source of bias (e.g. recall bias when medication use and/or falls are self-reported)

Potential limitations include the limited adjustment of lifestyle covariates such as smoking and alcohol drinking, which may have led to an over-estimation of the risk of fall. However, the results are consistent and similar to the results obtained from previous studies, which indicates that the estimates were not affected by lifestyle confounders. Implications of this study are included in the overall discussion chapter (Chapter 9).

7.6 Conclusion

In conclusion, the findings suggest that among patients with KOA, people who use analgesics are at an 89% greater risk of falling compared to patients not using any analgesics within one year after KOA diagnosis.

The study also found an escalation of the risk of fall in patients using multiple analgesics compared to those not using any within one year after KOA diagnosis. The risk of fall was 36 to 70% higher in patients using a single analgesic treatment group compared to those not using any. In patients using dual analgesic treatments, the risk was 1.99 to 2.24 times greater than in those who did not use any analgesics. The risk of fall was highest among users of all three analgesic treatment groups; they were at more than three times the risk of fall compared to those who did not use any analgesics: HR 3.24 (2.77, 3.78). These findings were consistent with findings reported in previous studies.

Chapter 8 Association Between Analgesic and Risk of Fall as a Time-Varying Analysis

8.1 Introduction

In the previous chapter of this thesis, the association between analgesic use and the risk of fall within one year of KOA diagnosis was examined. Patients who had used any analgesic were at a significantly greater risk of fall compared to those not using any analgesics within one year of KOA diagnosis (HR 1.89 (95% CI 1.66, 2.16)), adjusted for age, gender and the use of other FRIDs at baseline. The risk varied according to the analgesic groups used; patients using all three analgesic groups (neuropathic medications, opioid and non-opioid analgesics) were at the highest risk of fall: HR (95% CI) of 3.24 (2.77, 3.78) adjusted for age, gender and any use of FRIDs. However, analgesic use in patients with KOA may not always follow a regular pattern of daily use throughout their follow-up period. Patients often modify analgesic use to their lifestyle and pain intensity; hence, the risk of fall may vary according to current analgesic use status (see details below in 8.1.1).

In this chapter, the association between the current use of analgesics and the risk of fall is examined while treating analgesic use as a time-varying exposure.

8.1.1 Rationale for Treating Analgesic Use as a Time-Varying Exposure

Patients with OA exhibit various patterns of analgesic use, including switching to an alternative analgesic class, augmentation with another analgesic class or discontinuation of prescribed analgesics. In the UK, a study using data from The Health Improvement Network (THIN), a primary care database, reported that between 84% and 93% of patients with OA discontinue their first analgesic treatment within a period of 12 months after initiation, and between 8.7% and 15.2% use an additional analgesic shortly after initiation of their first analgesic class, while between 30% and 59.6% switch to an alternative class within the same period (Gore et al., 2012). The study included 6,639 and 542 people who had started to take NSAIDs and COX-2 initiators respectively and 3,215, 1,724 and 5,886 who had started to take paracetamol, tramadol and weak opioids respectively. Possible reasons for such changes were inadequate pain control or encountered adverse drug effects.

Against this background, there is a rationale for treating analgesic use as a time- varying exposure, as this accounts for patients changing treatments during follow-up and changing from treatment to no treatment. Furthermore, applying time-varying exposure/analysis will handle the immortal time bias (ITB) that is potentially present in crude time-fixed analysis. ITB occurs when there is variation in the timing of treatment initiation from cohort entry and time to treatment is ignored (Agarwal et al., 2018). ITB was first identified in the 1970s in epidemiology in cohort studies of the survival

benefits of heart transplantation (Gail et al., 1972). It recently surfaced in pharmacoepidemiology, with several studies reporting that various medications can be extremely effective at reducing morbidity and mortality; however, these studies involved some form of immortal time. For example, in a time-fixed analysis of the association between exposure to inhaled corticosteroids within 90 days after a hospital discharge for COPD and mortality, the adjusted rate ratio (95% CI) was 0.69 (0.55, 0.86), whereas the time-dependent rate ratio was 1.00 (0.79, 1.26). The rate ratios were affected by the length of exposure period, ranging from 0.98 for a 15-day exposure period to 0.51 for 365 days in the time-fixed analysis. However, they were stable between 1.06 and 0.94 respectively with time-dependent analysis. This example demonstrates that use of inhaled corticosteroids after hospitalisation for COPD did not reduce mortality and morbidity with appropriate immortal time analysis (Suissa et al., 2002).The difference in findings after immortal time analysis was also seen in studies of drug effectiveness in cardiovascular conditions and multiple sclerosis (Karim et al., 2016).

In examining the association between analgesic use and the risk of fall, it is not clear whether the application of time-varying analyses would result in different risk profiles of individual analgesic classes compared to time-fixed analysis. The most common approach to account for immortal time bias in observational studies is the adoption of time-dependent analyses such as time-dependent Cox proportional hazards models (Zhou et al., 2005).

8.1.2 Current Literature on Analgesic Use and the Risk of Fall

As discussed in Chapter 2 of this thesis, the association between analgesic use and the risk of fall has been examined in several studies; however, only a few of these studies have investigated medication use as a time-varying exposure (Bedson et al., 2019, Coupland et al., 2011, Modén et al., 2010, Söderberg et al., 2013). Coupland et al. (2011) investigated the safety of antidepressant drugs and found a significant association between antidepressant use and the risk of fall. On the other hand, Bedson et al. (2019) reported a significant association between current long-term opioid use and the risk of fall. However, these studies included patients with diagnosed depression and long-term opioid users respectively, and it is not known whether the analyses controlled for the use of other analgesics.

Previous work in this thesis (in Chapter 7) showed a significant association between exposure to any analgesic and the risk of fall using crude (time-fixed) analysis. Patients remain at risk of fall throughout the study period (12 months after KOA diagnosis) even during times prior to drug initiation (i.e. periods from the date of KOA diagnosis until drug prescribing) and regardless of subsequent analgesic use or non-use periods. It is not clear whether the risk varies during periods of analgesic use compared to periods of no-analgesic use within one year of KOA diagnosis.

This study sought to investigate the association between analgesic use and the risk of fall among patients with KOA within the first year of KOA diagnosis. Estimating the risk associated with the current use of medications in patients with KOA is crucial to inform policy makers as well as clinicians

in practice. Such information would inform, direct and intensify fall prevention initiatives around the times of medication use.

8.2 Study Aim and Objectives

The overall aim of this study was to assess the risk of falls associated with the use of analgesics, in order to provide evidence to support decision making by policy makers and clinicians when prescribing these classes of medications to individual patients with KOA in England.

Specific study objectives were:

1. To examine the association between current exposure to individual analgesic classes and the risk of fall for the following classes – antidepressants, AEDs, opioids, NSAIDs and paracetamol – compared to no-current exposure.
2. To establish the safety of the use of each analgesic class compared to non-use in relation to falls, among patients with KOA in England.
3. To compare the risk of fall in patients with KOA obtained from the two analytical approaches (time-fixed and time-varied analyses).

8.3 Methods

8.3.1 Study Design

This study used a retrospective cohort study design.

8.3.2 Study Population

The patients included in this study were those with a first computer-recorded diagnosis of KOA made between 1st Jan 2000 and 31st Dec 2014, and aged 18 years or older. The cohort was restricted to patients with a first recorded diagnosis of KOA so that analgesic prescribing would not be influenced by any previous record of KOA diagnosis. Patients were eligible for inclusion if their diagnosis of KOA occurred at least 12 months after registration with the GP practice. This period was required to ensure that KOA recording was not a retrospective recording of the diagnosis in the past, i.e. to minimise the inclusion of prevalent cases (Lewis et al., 2005). The included patients were also required to have a record in the CPRD with records linked to HES data, and each patient's entry date was defined as the date of KOA diagnosis in primary care. The start of follow-up was the latest of 12 months after current registration date or uts date (as detailed in Chapter 3).

8.3.3 Exposure

The main exposure of interest was treatment with analgesics. Details of all prescriptions for analgesics in the study cohort were gathered, following their earliest date of diagnosis of KOA (index diagnosis date between 1st Jan 2000 and 31st Dec 2014) up to 31 December 2015 or up to 12 months after KOA diagnosis, or date of death or leaving the practice if this was earlier. Analgesics were grouped into five exposure groups according to the analgesic class prescribed during the follow-up period, defined as the period

of 12 months after index KOA diagnosis. The drug classes included in the study were: antidepressants, AEDs, opioids, NSAIDs and paracetamol.

The duration of each prescription was calculated by dividing the total quantity dispensed by the numeric daily dose (as described in Chapter 5) and the number of treatment episodes per patient for each analgesic class was then determined. A treatment episode was defined as a period of analgesic use without gaps of more than 60 days between the end of a prescription (prescription's supply) and the start of the next prescription. A prescription after more than 60 days was counted as the start of a new treatment episode (refer to chapter 5 for the rationale of choosing the 60-day gap period).

The follow-up period was selected to be 12 months from the index date as there is evidence that the majority of primary care patients with a diagnosis of KOA switch, augment or discontinue their pain treatments 2–6 months after initiation (Gore et al., 2012). Hence a period of 12 months after KOA was selected to incorporate more periods of treatment (periods of analgesic use) and more events (falls) than a shorter follow-up (e.g. 2- or 6-months follow-up), thus avoiding any concerns over under-powering the study. The 12-month period also enabled comparison with the results of the crude analysis on the association between analgesic use and the risk of fall obtained from earlier work (see Chapter 7).

8.3.4 Outcome

Information on fall events was extracted from patients' records, using Read and ICD-10 codes of fall in the CPRD and HES databases (codes in Appendix 3 Table 3.1 and 3.2). The date of fall occurrence used in the analysis was the first recorded date of fall during follow-up, recorded either in their general practice or in-patient records.

8.3.5 Potential Confounding Variables

The following baseline variables were measured for each patient during the year prior to diagnosis:

1. Age: in years at the index diagnosis.
2. Gender: (male, female).
3. Patient-level deprivation score (as defined by the index of multiple deprivation (IMD) quintiles).
4. Previous falls (falls during the previous year as described in Chapter 7), this was a binary variable.
5. Comorbidities associated with an increased risk of fall (recorded in the year before the index date) were treated as a binary variable. These included the presence of any of the following conditions: depression, seizure disorders, coronary heart disease (CHD), diabetes, hypertension, stroke and chronic obstructive pulmonary disease (COPD). These were identified using appropriate Read codes in the patient records (clinical, consultation and referral files using code lists

available from the Quality and Outcome Framework (QOF) business rules as well as codes from Cambridge 2018 version 1). The period of one year was selected as patients with such chronic conditions would normally visit their GPs at least once a year, hence the period of one year prior to KOA would ensure the capture of updated comorbidities from patient records. Lists of the Read codes used are included in Appendix 1 Table 1.4.

6. The use of other analgesic classes (other than the class analysed) at baseline (within 12 months prior to the index diagnosis of KOA) was assessed within the multivariable analysis. Adjusting for the use of other analgesics (a binary variable) was done to examine whether the association between the use of any particular class and the risk of fall is independent of the use of other analgesics.

   The use of other FRIDs at baseline (a period of 12 months prior to the index diagnosis of KOA). This period was selected for measuring baseline parameters to ensure the inclusion of the most recently prescribed FRIDs. Like the use of other analgesics, the use of FRIDs was a binary variable.

   If any of the above potential confounding variables led to ≥ or ≤ 10% in the HR for analgesic exposure, it was retained in the multivariable model.

8.3.6 Statistical Analysis

For the primary statistical analysis, the Cox proportional hazards model was used to estimate the associations between the risk of fall and exposure to

analgesic drugs during the first year of KOA diagnosis, treating analgesic exposure as a time-varying exposure. Information on fall events during the first year after KOA diagnosis was extracted. The entry date in the analysis was the date of KOA diagnosis and the date of the first fall after KOA diagnosis was marked as the event date. Patients who did not experience any fall were censored at the earliest of: date of death, date of leaving the practice, the study end date or the end of the first year of follow-up.

Patients were classified as being exposed to a drug if there were no gaps of more than 60 days between the end of one prescription and the start of the next prescription, in order to allow for not having a precise date when a patient finished the prescription. If there were gaps of more than 60 days between the end of one prescription and the start of the next, then patients were counted as exposed to analgesics for the first 60 days and then unexposed for the remaining period.

The analysis calculated HR and (CI) for the current use of each separate class of analgesics (antidepressants, AEDs, opioids, NSAIDs and paracetamol) compared with no-current use.

The hazard ratio estimated from this analysis is interpreted as the ratio of the instantaneous rate of fall. The reference group was the no-current use category and this included periods of non-exposure in patients treated with analgesics as well as periods of non-exposure from patients who were not prescribed any analgesics over the follow-up period. Results were reported unadjusted and after adjusting for potential confounders.

The period of 12 months after the diagnosis of KOA was split into two 6-month periods from 0 to 6 months and from 6 to 12 months from the date of KOA diagnosis. This was done because there was some evidence of non-proportional hazards over one year of follow-up, seen as crossing log-log curves on at least one point. The split of the follow-up period was also done to investigate changes in hazard ratios over time since the first KOA diagnosis.

Age was tested as a continuous variable and as categorical variable, where age at diagnosis was grouped into 4 ranks (<40, 40–64, 65–80,>80 years). Categorisation into age groups was done to stratify the risk across age groups. The strategy used for identifying confounding variables was:

1. Fit a model with the exposures of interest.
2. Conduct a univariate analysis: In the model of step 1, each of the potential confounders were added one at a time, in a sequential manner (one potential confounder was removed before the next was added). If any of these potential confounders changed the effect of the exposure by more than, less than or equal to 10%, then this variable was considered in the fully adjusted model in step 3.
3. Fit the fully adjusted multivariable Cox proportional regression model using the variables from step 2 that were identified as confounders.

The steps carried out prior to running the main survival analysis included a graphical assessment of survivor function and statistical testing of the equality of survivor function. Proportional hazard assumption was checked by Schoenfeld residuals.

8.4 Results

This study included 57,383 patients who were diagnosed with KOA between Jan 1st 2000 and 31st December 2014 and had HES-linked records. A total of 465,536 analgesic prescriptions were prescribed within the first year of KOA diagnosis. The number of patients prescribed each drug class as well as the number of prescriptions are presented in Tables 8-1 and 8-2.

Table 8-1 Number of Patients and Prescriptions within One Year of KOA Diagnosis by Analgesic Class

Analgesic class	**Number of Patients (%) N=57,383**		**Number of Prescriptions (%) N=465,536**	
Antidepressants	11,569	20.1	97,545	20.9
AEDs	2,635	4.5	26,687	5.7
Opioids	26,997	47.0	176,802	37.9
NSAIDs	20,473	35.6	82,347	17.6
Paracetamol	16,007	27.8	82,155	17.6

AEDs: Antiepileptic drugs NSAIDs: non-steroidal anti-inflammatory drugs

Table 8-2 Details of the Number of Prescriptions Received within One Year of KOA Diagnosis by Analgesic Class

Prescriptions	**Antidepressant users n=11,569**		**AED users n=2,635**		**Opioid users n=26,997**		**NSAID uses n=20,473**		**Paracetamol n=16,007**	
	n	**%**	n	**%**	n	**%**	n	**%**	n	**%**
1	2,091	18.1	422	16.0	7,108	26.3	7,270	35.5	4,639	28.9
2–6	3,878	33.5	849	32.2	10,638	39.4	8,931	43.6	6,757	42.2
7–12	3,194	27.6	670	25.4	5,074	18.8	3,437	16.8	3,408	21.3
>12	2,406	20.8	694	26.4	4,177	15.5	835	4.1	1,214	7.6

AEDs: Antiepileptic drugs NSAIDs: non-steroidal anti-inflammatory drugs

Within the study population of patients with diagnosed KOA, 47% were prescribed opioids during the first year after diagnosis (n=26.997) and 35% (n=20,473) were prescribed NSAIDs, while less than 5% were prescribed AEDs (4.59% n=2,635) (Table 8-1). Of those prescribed antidepressants within the first year of KOA diagnosis, 18% were prescribed once (n=2,091 out of 11,569), while 20.8% had more than 12 prescriptions (n=2,406 out of 11,569 patients). Table 8-2 shows that a quarter of those prescribed opioids were prescribed once (26.3% n=7,108 out of 26,997 patients) and 15% had more than 12 opioid prescriptions within the first year of KOA diagnosis (n=4,177 out of 26,997). A single AED prescription was received by only 16% of those prescribed AEDS, while a single NSAID prescription was received by 35% of those prescribed NSAID and by 28% of those prescribed paracetamol (Table 8-2).

Table 8-3 shows the number of follow-up days by analgesic class. Among patients in this cohort, those who used AEDs had the longest duration of follow-up with a median of 365 days (IQR 289,365), followed by antidepressants with 363 days (IQR 269,365).

Table 8-3 Follow-up Days by Analgesic Class

Analgesic Class	**Median Days of Follow-up**	**IQR**
Antidepressants	363	269,365
AEDs	365	289,365
Opioids	308	151,365
NSAIDs	266	97,364
Paracetamol	316	170,363

AEDs: Antiepileptic drugs, NSAIDs: non-steroidal anti-inflammatory drugs, IQR: Inter Quartile Range

8.4.1 Patient Characteristics

Across the studied analgesic classes, females constituted the majority of users (>60%), and the mean age of paracetamol users was higher compared to users of other analgesic classes. The sociodemographic and clinical characteristics of patients with KOA by analgesic class are presented in Table 8-4.

Table 8-4 Characteristics of Study Cohort (n=57,383) Stratified by Drug Class. Values are Numbers of Patients (%) Unless Stated Otherwise

	Antidepressant	**AED**	**Opioid**	**NSAIDs**	**Paracetamol**
	n=11,569	n=2,635	n=26,997	n= 20, 473	n= 16,007
Females (%)	8,488 (73.3)	1,704 (64.6)	17,227 (63.8)	12,297(60.0)	10,635 (66.4)
Mean age, years (SD)	67.03 (13.65)	65.77 (12.92)	68.22 (12.49)	66.6 (11.61)	73.80 (11.64)
Age groups, years (% from total prescribed respective drug class)					
>40	239 (2.1)	41 (1.6)	342 (1.3)	398 (1.9)	105 (0.7)
40─64	5,228 (45.2)	1,175 (44.6)	10,542 (39.0)	9,372 (45.8)	3,797(23.7)
65─80	4,113 (35.5)	1,015 (38.5)	11,317 (41.9)	8,201 (40.1)	7,481(46.7)
>80	1,989 (17.2)	404 (15.3)	4,796 (17.8)	2,511 (12.2)	4,624(28.9)
IMDs score					
1 (least deprived)	2,099 (18.1)	428 (16.2)	4,836 (17.9)	4,124 (20.1)	2,767 (17.3)
2	2,472 (21.4)	576 (21.9)	5,962 (22.1)	4,666 (22.8)	3,582 (22.4)
3	2,411 (20.8)	515 (19.5)	5,523 (20.5)	4,428 (21.6)	3,498 (21.8)
4	2,402 (20.8)	558 (21.2)	5,613 (20.8)	3,997 (19.5)	3,331 (20.8)
5	2,177 (18.8)	556 (21.1)	5,050 (18.7)	3,249 (15.9)	2,825 (17.6)
Not recorded	8 (0.1)	2 (0.1)	13 (0.05)	9 (0.1)	4 (0.1)
Comorbidities at baseline					
Cardiovascular disease	930 (8.0)	179 (6.8)	2,286 (8.5)	1,464 (7.1)	1,508 (9.4)
Diabetes	463 (4.0)	106 (4.0)	1,074 (3.9)	649 (3.1)	692 (4.3)
COPD	262 (2.3)	67 (2.5)	529 (1.9)	228 (1.1)	307 (1.9)

Epilepsy	115 (1.0)	443 (16.8)	252 (0.9)	160 (0.7)	191 (1.1)
Stroke	124 (1.1)	44 (1.7)	212 (0.7)	100 (0.4)	171 (1.0)
Depression	1,790 (15.4)	187 (7.1)	1,424 (5.2)	965 (4.7)	752 (4.6)
Other characteristics at baseline					
Using FRID	7,812 (67.5)	1,883 (71.5)	17,712 (65.6)	11,306 (55.2)	11,300 (70.5)
Using analgesics*	9,948 (86.0)	2,402 (91.2)	19,417 (71.9)	14,532 (70.9)	12,471(77.9)
Previous fall	1,432 (12.4)	379 (14.4)	2,790 (10.3)	1,392 (6.7)	2,020 (12.6)

*analgesics other than the studied class FRID**:** fall risk increasing drugs; IMD: index of multiple deprivation; AEDs: Antiepileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; COPD: Chronic Obstructive Pulmonary Disease; SD: standard deviation

Table 8-5 Analgesic Treatment Episodes within the First Year after KOA Diagnosis

No. of episodes	**Antidepressant** n=11,569		**AED** n=2,635		**Opioid** n=26,997		**NSAID** n=20,473		**Paracetamol** n=16,007	
	n	%	n	%	n	%	n	%	n	%
1	9,773	84.5	2,396	90.9	19,162	70.9	15,542	75.9	10,839	67.7
2	1,566	13.5	213	8.1	6,120	22.7	4,189	20.5	3905	24.4
≥3	215	2.0	26	1.0	1,715	6.4	742	3.6	1136	7.9
Duration of analgesic treatment per treatment episode (days)										
Median (IQR)	294 (83,347)		309 (100,350)		185 (17,333)		133 (28,318)		199 (25,328)	

AEDs: Antiepileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; IQR: Inter Quartile Range

8.4.2 Cox Proportional Regression with Analgesic Use Over One Year Defined as a Time-Varying Exposure

The following section reports the results of the main analysis by applying a Cox proportional model for the association between analgesic use within one year after KOA diagnosis and the risk of fall. The section starts by presenting the results of the unadjusted HR (95% CI) followed by the steps

carried out prior to running the final multivariable analysis, including: the graphical assessment of survivor function, the statistical testing of the equality of survivor function and the graphical testing of proportional hazard assumption. The section closes by presenting the results of the adjusted HR (95% CI) for individual analgesic classes.

8.4.2.1 Cox Proportional Hazards Regression Model with Analgesic Use

A separate model was applied for each analgesic class and the respective hazard ratios unadjusted (95% CI) are presented in Table 8-6. The unadjusted HRs (95% CI) showed a significant association between analgesic use and the risk of fall across classes and over both intervals of follow-up, i.e. from the time of KOA diagnosis until 6 months and from 6 to 12 months of KOA diagnosis (Table 8-6).

Table 8-6 Current Use of Analgesics and the Risk of Fall

Analgesic Class	HR-Unadjusted	95% CI	P-Value
0-6 months of KOA diagnosis			
No current treatment	Reference	-	-
Antidepressants	2.50	2.17–2.98	< 0.0001
AEDs	2.01	1.53–63	< 0.0001
Opioids	3.11	2.74–3.53	< 0.0001
NSAIDs	1.70	1.45–2.00	< 0.0001
Paracetamol	3.61	3.13–4.16	< 0.0001
6-12 months of KOA diagnosis			
No treatment	Reference	-	-
Antidepressants	2.30	1.98–2.69	< 0.0001
AEDs	2.02	1.55–2.65	< 0.0001
Opioids	2.58	2.26–2.94	< 0.0001
NSAIDs	1.51	1.27–1.79	< 0.0001
Paracetamol	3.31	2.88–3.84	< 0.0001

AEDs: Antiepileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; HR: hazard ratio; CI: confidence interval

8.4.2.2 Graphical and statistical Assessment of Survivor Function

The KM curves for failure functions were generated for each analgesic drug class (Appendix 4 & 5). The log rank test was performed to test the equality of survivor function for both intervals (0–6 and 6–12 months of the diagnosis of KOA). The p-values were statistically significant ($p<0.001$), which implies the null hypothesis that the risk of fall was the same during periods of analgesic use and non-use of each analgesic class must be rejected.

8.4.3 Impact of Potentially Confounding Variables on the Risk of Fall (Univariate Analysis)

Each potential confounder was added to the Cox regression model separately and sequentially one at a time, as described in section 8.3.5 of this chapter. The p-values obtained from the univariate analyses were significant ($p<0.05$), except for the effect of the IMD score, which had statistically insignificant p-values ($p>0.05$) and CIs crossing 1

The effect of confounders varied across classes and follow-up intervals; hence, separate models were developed for each class with adjustments such that confounders significantly affecting (exerting a change of ±10%) the unadjusted HR were included in the final adjusted model for that particular class. Table 8-7 shows the confounders adjusted for within each class, and Table 8-8 contains the effect of each confounder.

Table 8-7 Confounders Adjusted for in the Final Multivariate Model of Respective Analgesic Class

Drug Class	**Confounders Adjusted for in the Final Multivariate Model**	
	0–6m	6–12 m
Antidepressants	Gender, FRID, use of other analgesics	Gender, FRID, use of other analgesics
AEDs	Age, comorbidity, FRIDs	Age
Opioids	Age, FRIDs, use of other analgesics	FRIDs, use of other analgesics
NSAID	None	Age
Paracetamol	Use of other analgesics	Age, FRIDs

AEDs: Antiepileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; FRID fall risk increasing drugs

Table 8-8 The Effects of Confounders on HR for Fall

Class	Antidepressant	AEDs	Opioids	NSAID	Paracetamol
0-6 months					
HR Unadjusted (95%CI)	2.52 (2.17–2.89)	2.01 (1.53–2.63)	3.11 (2.74–3.53)	1.70 (1.45–2.00)	3.61 (3.13–4.16)
Gender	2.27 (1.96–2.62)	1.94 (1.48–2.54)	2.92 (2.60–3.35)	1.69 (1.45–1.99)	3.40 (2.95–3.92)
Age	2.54 (2.2.–2.94)	2.21 (1.69–2.90)	2.89 (2.54–3.27)	1.95 (1.66–2.29)	2.44 (2.11–2.81)
Comorbidity	2.35 (2.03–2.72)	1.77 (1.35–2.32)	3.01 (2.68–3.45)	1.71 (1.46–2.00)	3.50 (3.05–4.06)
Previous fall	2.46 (2.12–2.84)	1.93 (1.48–2.53)	3.06 (2.70–3.47)	1.73 (1.47–2.03)	3.50 (3.04–4.05)
Use of FRIDs	2.27 (1.97–2.63)	1.82 (1.39–2.38)	2.82 (2.48–3.20)	1.70 (1.45–1.99)	3.19 (2.77–3.68)
IMD score					
1	2.50 (2.17–2.89)	2.18 (1.66–2.85)	3.11 (2.74–3.53)	1.70 (1.45–2.00)	3.59 (3.11–4.14)
2	1.07 (0.89–1.29)	1.08 (0.90–1.31)	1.04 (0.86–1.25)	1.08 (0.90–1.31)	1.06 (0.88–1.27)
3	1.12 (0.93–1.36)	1.15 (0.95–1.39)	1.09 (0.91–1.32)	1.16 (0.96–1.40)	1.11 (0.92–1.34)
4	1.23 (1.02–1.49)	1.27 (1.05–1.53)	1.17 (0.97–1.42)	1.28 (1.06–1.55)	1.22 (1.01–1.47)
5	1.08 (0.88–1.33)	1.13 (0.92–1.39)	0.99 (0.81–1.22)	1.15 (0.94–1.42)	1.06 (0.86–1.30)
Use of other analgesics	1.56 (1.28–1.90)	1.41 (0.92–2.18)	2.55 (2.22–2.93	1.58 (1.31–1.89)	2.45 (2.07–2.90)
6-12 months					
HR Unadjusted (95% CI)	2.31 (1.98–2.69)	2.02 (1.55–1.65)	2.58 (2.26–2.94)	1.51 (1.27–1.79)	3.31 (2.88–3.84)
Gender	2.11 (1.81–2.46)	1.97 (1.51–2.58)	2.46 (2.16–2.81)	1.50 (1.26–1.78)	3.15 (2.73–3.64)
Age	2.35 (2.01–2.73)	2.22 (1.70–2.91)	2.47 (2.16–2.82)	1.71 (1.44–2.04)	2.38 (2.01–2.75)
Comorbidity	2.25 (1.93–2.62)	1.89 (1.44–2.48)	2.54 (2.23–2.90)	1.51 (1.27–1.80)	3.27 (2.83–3.78)
Previous fall	2.23 (1.92–2.60)	1.93 (1.49–2.53)	2.51 (2.20–2.87)	1.54 (1.29–1.83)	3.21 (2.78–3.71)
Use of FRIDs	2.13 (1.83–2.49)	1.84 (1.41–2.42)	2.36 (2.07–2.70)	1.50 (1.26–1.78)	2.98 (2.58–3.45)
IMD score	2.33 (2.00–2.71)	2.04 (1.55–2.67)	2.61 (2.29–2.98)	1.51 (1.27–1.79)	3.34 (2.89–3.86)
2	1.05 (0.88–1.26)	1.07 (0.90–1.28)	1.06 (0.89–1.27)	1.07 (0.90–1.28)	1.06 (0.89–1.26)
3	1.03 (0.86–1.25)	1.06 (1.88–1.26)	1.03 (0.86–1.24)	1.05 (0.88–1.26)	1.02 (0.89–1.26)
4	0.99 (0.82–1.20)	1.01 (0.84–1.22)	0.97 (0.80–1.17)	1.02 (0.85–1.23)	0.98 (0.81–1.18)
5	0.88 (0.71─1.09)	0.95 (0.77─1.16)	0.89 (0.72─1.09)	0.96 (0.78─1.18)	0.91 (0.74─1.12)
Use of other analgesics	2.86 (2.28─3.60)	1.08 (0.72─1.62)	2.07 (1.79─2.39)	1.34 (1.11─1.63)	2.23 1.88─2.64

AEDs: Antiepileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; FRID: fall risk increasing drugs; IMD: index of multiple deprivation; HR: hazard ratio; CI: confidence interval

8.4.4 The Final Adjusted Models

The risk of fall with current analgesic use remained significantly greater than that for non-use for all analgesic classes, but varied by analgesic class and across both follow-up intervals (Table 8-9). Within the first interval (0–6 months from KOA diagnosis), adjusting for important confounders changed the HRs for falls with all analgesic classes. The change was greatest for antidepressants, opioids and paracetamol, while it was minimal for NSAIDs (Table 8-9). The association between the current use of AEDs and the risk of fall was found to be insignificant after adjusting for the use of other analgesics, age at KOA diagnosis and the existence of at least one comorbidity at baseline (HR-adjusted 1.40 [95% CI 0.91, 2.16] p>0.05).

The HRs for the second follow-up interval (6–12 months from KOA diagnosis) were similar to those in the first interval and as in the first interval, changes were seen in the HRs after adjusting for important confounders (Table 8-9). However, the changes were most pronounced for paracetamol, opioids and antidepressants, which showed an increase in the risk of fall after adjusting for gender, the use of FRIDs and the use of other study analgesics (HR [95% CI] 2.31[1.98, 2.69] to 2.68 [2.14, 3.36]). Unlike the first interval, the association between current use of AEDs and the risk of fall was significant and remained so after adjustment for confounding by age at KOA diagnosis (2.02 [1.55, 1.65] to 2.22 [1.70, 2.91]). Across analgesic classes within 6 months of KOA diagnosis, the current use of opioids was associated with the greatest risk of fall versus no use (HR-adjusted [95% CI] 2.40 [2.01, 2.85]) compared to the current use of antidepressants,

NSAIDs and paracetamol (HR-adjusted [95% CI]) of (1.46 [1.20, 1.78], 1.72 [1.43, 2.07], 1.98 [1.68, 2.33] respectively). Subsequently, the association between current opioid use and the risk of fall was attenuated in the second 6-month period with HR-adjusted (95% CI) of 1.96 (1.70, 2.26). However, it remained significant. Similarly, the association between current use of NSAIDs and paracetamol was slightly attenuated but remained significant (from 1.72 [1.43, 2.07] to 1.96 [1.70, 2.26] for NSAIDs and from 1.98 [1.68, 2.33] to 1.47 [1.21, 1.78] for paracetamol) across both follow-up intervals.

Between 6 and 12 months after KOA diagnosis, the greatest risk of fall was associated with the current use of antidepressants followed by AEDs: HR-adjusted (95% CI) of 2.68 (2.14, 3.36) and 2.22 (1.70, 2.91) respectively. In fact, unlike opioids, NSAIDs and paracetamol, for which the HRs lowered in the second follow-up interval, the adjusted HRs for antidepressants and AEDs increased in the second interval compared to the first interval, from 1.46 (1.20, 1.78) to 2.68 (2.14, 3.36) for antidepressants and from 1.40 (0.91, 2.16) to 2.22 (1.70, 2.91) for AEDs.

The proportional hazard assumption was tested using Schoenfeld residuals and the p-value was found not significant (p=0.38). this implied that the PH assumption was not violated.

Table 8-9 Association between Analgesic Use and the Risk of Fall

	Unadjusted			**Adjusted**		
0–6 months						
	HR	95% CI	p-values	HR	95% CI	p-values
No current use	1.0	Reference	Reference	1.0	Reference	Reference
Antidepressants	2.52	2.17–2.89	<0.001	1.46	1.20–1.78	<0.001
AEDs	2.01	1.53–2.63	<0.001	1.40	0.91– 2.16	0.122
Opioids	3.11	2.74–3.53	<0.001	2.40	2.01– 2.85	<0.001
NSAIDs	1.70	1.45–2.00	<0.001	1.72	1.43– 2.07	<0.001
Paracetamol	3.61	3.13–4.16	<0.001	1.98	1.68– 2.33	<0.001
6-12 months						
No current use	1.0	Reference	Reference	1.0	Reference	Reference
Antidepressants	2.31	1.98–2.69	<0.001	2.68	2.14–3.36	<0.001
AEDs	2.02	1.55–1.65	<0.001	2.22	1.70–2.91	<0.001
Opioids	2.58	2.26–2.94	<0.001	1.96	1.70–2.26	<0.001
NSAIDs	1.51	1.27–1.79	<0.001	1.47	1.21–1.78	<0.001
Paracetamol	3.32	2.88–3.84	<0.001	1.92	1.63–2.26	<0.001

AEDs: Antiepileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; CI: confidence interval; HR: hazard ratio

8.5 Discussion

8.5.1 Main Findings by Analgesic Class

This cohort study estimated the risk of fall associated with current exposure to individual analgesic classes, adjusting for potential confounding variables. The current use of all studied analgesic classes was associated with an increased risk of fall compared to periods of no use in this cohort of patients diagnosed with KOA. The risk was more than 2-fold higher in people currently using opioids, antidepressants AEDs or paracetamol, and up to 72% higher in those currently using NSAIDs. Fall risk varied across follow-up intervals and showed a stronger association with the current use of opioids, NSAIDs and paracetamol in the first 6 months after KAO diagnosis. On the other hand, the current use of antidepressants and AEDs showed a stronger association with the risk of fall within the period 6–12 months after KOA diagnosis.

8.5.2 Comparison with Other Studies

In this sub-section, comparisons with published studies are made for each class separately. The present study found an association between the current use of antidepressants and the risk of fall with HR-adjusted (95% CI) of 1.46 (1.20, 1.78) and 2.68 (2.14, 3.36) within 6 and 12 months of KOA diagnosis respectively. These findings were similar to those reported in a population-based cohort study using UK primary care data from general practices contributing to the QResearch database (Coupland et al., 2011).

Coupland et al. (2011) reported an increased risk of fall with current antidepressant use compared with when no antidepressants were being used. The reported HRs (95% CI) were 1.66 (1.58, 1.73) for SSRIs, 1.39 (1.28, 1.52) for other antidepressants and 1.30 (1.23, 1.38) for tricyclic antidepressants.

Similarly, a case-control study in UK primary care using data from the THIN database found that there was an increased risk of fall with the current prescribing of serotonin norepinephrine reuptake inhibitors (SNRIs) (adjusted OR [95% CI] of 1.79 [1.42, 2.25]) in fall cases compared to controls (Gribbin et al., 2011). However, both studies included patients aged 60 years or older who were diagnosed with depression, and hence, the estimated risks may be different in people with painful conditions such as KOA.

The reported risk of fall in the second 6-month interval within the present study was higher than that reported by Coupland et al. (2011). This could be explained by the shorter follow-up period compared to a follow-up of 5 years in Coupland et al.'s study, resulting in a smaller number of treatment and no-treatment periods, potentially leading to an over-estimation of the association.

The association between gabapentin and pregabalin use (time-varying exposure) and the risk of fall was investigated in a recent study using the US Renal Data System. The current use of gabapentin at daily doses between 100mg and 200mg was associated with a significant increase in

the risk of fall: HR 1.35 (95% CI 1.15, 1.57). Similarly, the use of pregabalin was also associated with an increased risk of fall: HR 1.68 (95% CI 1.36, 2.08) at doses greater than 100mg per day (Ishida et al., 2018). Despite being consistent with findings from the present study, which reported HR 2.22 (95% CI 1.70, 2.91), the study by Ishida et al. (2018), was carried out in patients receiving haemodialysis in 2011, which may be different to the population of the present study. Hence, this difference in population needs to be considered when comparisons are made or when interpreting the results.

The present study showed an association between the current use of opioids and the risk of falls throughout the year after KOA diagnosis; however, the association was stronger earlier in the follow-up period compared to the later 6–12 months. This may be explained by findings from prior studies that have identified the period of 1–85 days as a high-risk period for sustaining a fall. Moden et al. (2010), in a nested case-control study, showed that the odds of falling within the period of 1–85 days were 1.90 (1.49, 2.42) in males and 1.92 (1.68, 2.20) in females in this population-based study (Modén et al., 2010). Additionally, Soderberg et al. (2013), in a population-based case-crossover study from Sweden, identified the period of the first 28 days after opioid initiation as a high-risk period for sustaining a fall-related injury. HR (95% CI) was 2.85 (2.74, 3.00) 28 days after treatment was initiated (Söderberg et al., 2013). Moreover, the authors showed that the risk was highest in patients who used opioids 1–7 days before the fall date, compared to those who used opioids within 8–85 days.

The effect size estimates were OR (95% CI) 6.07 (2.64, 3.99) in males and 5.16 (3.11, 8.56) in females, compared to 1.37 (1.07, 1.75) and 1.53 (1.33, 1.76) in males and females respectively. Similarly, the risks were more pronounced during the first week after the start of treatment than during the three consecutive weeks and the reported estimates were 5.14 (4.76, 5.55), 2.57 (2.35, 2.81) 1.46 (1.31, 1.62) and 1.23 (1.10, 1.38) for weeks 1 to 4 respectively (Söderberg et al., 2013). It is possible that the greatest risk related to opioid treatment is after initiation and is due to opioids causing sedation, dizziness and cognitive impairment, all of which are risk factors for falls (Li et al., 2013).

The recent study by Bedson et al. (2019) reported a higher risk of fall during episodes of long-term use of opioids: HR (95% CI) 1.23 (1.19, 1.28) compared to non-long-term use (Bedson et al., 2019). These estimates were lower than those from the present study for the association between current opioid use and the risk of fall within the first 6 months (HR 2.40 [95% CI] 2.01, 2.85). The lower risk in Bedson's work can be explained by the fact that fall events were captured after long-term use was established (i.e. after 90 days of use) which meant that events which occurred after opioid therapy initiation were not included.

The association between the use of NSAIDs and paracetamol and the risk of fall is less well studied compared to other analgesics and limited research exists for comparisons. Moreover, the available studies have analysed exposure to NSAIDs and paracetamol as a time-fixed variable and therefore could not be compared to results from the present study. The findings from

the present study showed that the current use of NSAIDs was significantly associated with an increased risk of falls in the study population of patients with KOA with HR (95% CI) of 1.72 (1.43, 2.07) and 1.47 (1.21, 1.78) within 6 and 12 months of KOA diagnosis, respectively.

8.5.3 Interpretation of Results for Time-Varying Analysis in Context

The results from the present study were consistent with findings from the crude analysis. The crude analysis results showed a significant association between use of any analgesic and the risk of fall within one year of KOA diagnosis with HR-adjusted (95% CI) of 1.89 (1.66, 2.16), adjusted for age, gender and the use of other FRIDs. The findings of the present study quantified the risk associated with the current use of each specific analgesic class and within each 6-monthly interval from KOA diagnosis, revealing an increased risk of fall from 46% up to 2-fold higher during treatment, compared to when no treatment was being used.

The comparison of the risk estimates obtained from the crude analysis with the estimates from the time-varying analysis provides important insights into fall risks for individual drug classes. Current antidepressant and AED use within the first 6 months of KOA diagnosis (HR 1.46 [95% CI 1.20, 1.78] and 1.40 [95% CI 0.9, 2.16]) was associated with a lower risk of fall than the estimates from the crude analysis on the use of neuropathic pain medications (NP), HR 1.70 (95% CI 1.30, 2.23). However, the current use of antidepressants and AEDs in the second 6-month period after KOA

diagnosis was associated with a higher risk compared to the estimates from the crude analysis (HR [95% CI] for antidepressants 2.68 [2.14,3.36] and AEDs 2.22 [1.70, 2.91]).

The current use of opioids was associated with a greater risk of fall throughout the period of one year after KOA diagnosis, with risk estimates.

The findings from the time-varying analysis therefore add to and complement those obtained from the crude analysis. Taken together, these results convey a clear message on the need to prioritise patients with KOA taking analgesics for fall risk assessment, management and prevention strategies, in order to achieve optimal care and safety within this vulnerable group of patients.

8.5.4 Strengths and Limitations

8.5.4.1 Strengths

This study has a number of strengths. It is a large study, including more than 57,000 patients diagnosed with KOA. This study size allowed the inclusion of sufficient numbers within each analgesic class to study associations with the risk of fall; this may not have been possible with clinical trials, which are generally smaller and conducted over shorter follow-up periods. The study also had broad inclusion criteria and was population based rather than hospital based; hence, the findings are generalisable to all patients with KOA. This is again in contrast to clinical trials, which generally have strict

inclusion and exclusion criteria, resulting in the exclusion of many patients who have comorbidities.

Because data in the CPRD database are recorded prospectively, recall bias was eliminated. This study analysed the association between exposure to a relatively wide spectrum of drugs, most of which are recommended by clinical guidelines (NICE, 2014) and commonly prescribed by GPs, with the risk of fall, while adjusting for a number of confounders. The study adjusted for history of fall within one year prior to KOA, which means that the estimated risk includes patients who had experienced a previous fall. In this study, analgesic use was treated as a time- varying exposure and this relates the risk of fall to the analgesic drug class currently being used, rather than basing the results on other analgesic use patterns such as the first analgesic prescribed after KOA diagnosis or after long-term use. This is particularly important in the context of KOA, a chronic condition in which patients are likely to switch between analgesics or step up to stronger analgesics such as strong opioids (Foy et al., 2016).

8.5.4.2 Limitations

The main concerns with observational studies (such as the present study) are indication and ascertainment bias. Indication bias is found when medications are prescribed for a condition that is itself associated with the outcome of interest. This means that the observed association with a medication use may be owing to the condition for which it was prescribed, rather than to the medication itself (Kyriacou and Lewis, 2016).

KOA itself is associated with the adverse outcome of interest, fall; however, to reduce indication bias, this study's cohort was restricted to patients with a recorded diagnosis of KOA, and hence, all patients were likely to have a similar degree of severity of KOA (Jordan et al., 2016). Additionally, the use of other analgesics and FRIDs was adjusted for in the analysis. In the present study, the analysis was adjusted for a number of factors that could differ between the groups and which are risk factors for falls, including age, gender, comorbidity and the use of other FRIDs. Additionally, there may be other confounders that were not adjusted for in the present study, such as alcohol intake. Alcohol has long been considered as a risk factor for falls; however, a number of published studies have failed to confirm this assumption (Mukamal et al., 2004). Another concern is the channelling bias, whereby different analgesics might be prescribed according to individual patient's characteristics. For example, AEDs might have been preferentially prescribed rather than antidepressants to fragile patients who were at greater risk of falling. To minimise the potential channelling bias, adjustments were made in the analysis for confounding factors such as previous fall and the use of other analgesics at baseline. Nevertheless, it was not possible to eliminate the potential residual confounders in this cohort study.

The diagnosis of fall was not validated in the present study; however, data from CPRD have been previously used to examine the association between medication use and the risk of adverse events. For example, Bedson et al. used CPRD data to investigate the association between long-term opioid

use and the risk of adverse outcomes, including falls (Bedson et al., 2019). Additionally, several other primary care databases have been used to investigate the association between medication use and falls, including the QResearch and THIN databases, which were used to investigate the association between exposure to antidepressants and the risk of fall, along with other adverse outcomes (Gribbin et al., 2011, Coupland et al., 2011). The validity of diagnoses in CPRD was examined in a systematic review including 183 different diagnoses. It reported an overall high estimate of validity as the median proportion of cases with a confirmed diagnosis was 89% (Herrett et al., 2010).

Analgesic use varies with the severity of KOA pain, which in turn varies over time. However, pain severity is not captured in CPRD, and therefore the study adjusted only for confounders not changing over time, which could have introduced a bias in the results. Prescription data in CPRD are reliably recorded; however, analgesics received during hospitalisation episodes were not included. As the majority of people with KOA are managed in primary care, this should not have had much effect on the study's findings.

8.5.5 Study Implications

8.5.5.1 Implications for Practice and Policy

It is important to understand that the risk of fall differs between periods of medication use compared to non-use periods. The findings from the present study call for optimised fall-prevention strategies during periods of

medication use in patients with KOA. Keeping patients and practitioners informed of the heightened risk of fall during periods of medication use will optimise self-care of fall prevention.

8.5.5.2 Implications for Research

Research to confirm the findings from this study are needed, with consideration of longer follow-up periods (beyond 12 months from KOA diagnosis) to reveal the much-needed information on the long-term safety of these drugs. Additional studies looking into the risk of fall in relation to the dose prescribed (to explore any dose- response relationship) are needed to inform practice and the pharmaceutical industry, who may be keen to enforce pharmacovigilance activities.

8.6 Conclusion

The present study quantified the risk associated with the current use of analgesics within one year of KOA diagnosis. The study found an association between current analgesic use and the risk of fall across all classes. The association varied between the two 6-month intervals of the year. Antidepressants and AEDs showed a stronger association within the second 6-month interval, while opioids, NSAIDs and paracetamol showed a stronger association within the first 6-month interval. These findings have considerable implications for practice as the reported significant association with the current use of NSAIDs and paracetamol has generally not been explored/quantified previously in patients with KOA.

Chapter 9 General Discussion and Implications

This chapter summarises the key results obtained from the research studies in the thesis, followed by a section on overall strengths and limitations. The chapter also includes sections on the implications of findings for clinical practice, policy and future research, and finally closes with an overall conclusion.

9.1 Summary of Key Results

Key results obtained from studies in this thesis are presented sequentially in the order of previous chapters.

In Chapter 3, the overall study cohort of patients with KOA was selected from the CPRD with the application of diagnosis-based Read codes. The selected cohort included 137,051 patients with a clinician-recorded KOA diagnosis between 2000 and 2015, and females constituted 58.3% of them. The incidence of KOA diagnosis was measured annually between the years 2000 and 2015, and ranged between 1.33 and 1.45 patients per 1000 CPRD registrants. This was generally in agreement with the incidence rates reported in other European countries such as the Netherlands.

In Chapter 4, the temporal changes in the utilisation of five different classes of analgesic drugs by primary care patients with KOA were studied over a period of 16 years (between 2000 and 2015). Results showed a steady

increase in the prevalence of prescribing of the study drugs throughout most of the study years and across all classes, except for NSAIDs. In particular, the use of opioids was most prevalent, and compared with other classes, opioids had the highest number of prescriptions per 1000 CPRD registrants in every study year. Furthermore, from 2000 to 2014 the annual number of opioid prescriptions increased by 69% from 27 to 46 prescriptions per 1000 registrants. Within opioids, tramadol prescribing was most prevalent, and from 2000 to 2015 the number of DDDs increased from 0.11 to 0.64 DDDs per 1000 registrants per day. The study also used OMEQ as a unit of measure of prescribing prevalence, and from 2000 to 2014 demonstrated the increase in the number of OMEQ doses on an annual basis from 32.6 to 71.7 mg/day. The greatest increase in prescribing prevalence was observed for AEDs, with an increase from 2 to 11 prescriptions per 1000 registrants from 2000 to 2014. The number of new AED users also increased from 0.1 to 0.3 per 1000 registrants from 2000 to 2014.

In Chapter 5, the cumulative dose used by patients with an incident diagnosis of KOA was measured as DDD per patient per year. Additionally, the distribution of prescriptions within the quarters of the year after first initiation of the respective analgesic was determined. Accordingly, the proportions of persistent users were determined, and found to range between 36% (antidepressants) and 14.9 % (opioids). While the higher proportion of persistent antidepressant users identified in the study may indicate a better adherence to depression management within the KOA patient population, the proportion of persistent opioid users is of concern.

The concern stems from the fact that persistence was measured using two attributes of persistence (distribution of prescriptions, indicating continued use, and dose level), which means that these patients used opioids through three quarters of the year, and at cumulative doses, adding up to more than 180 DDDs. Additionally, persistence was measured during the first year after initiation, when more than half of opioid users had initiated therapy with a weak opioid. Evidence suggests that primary care patients with a definitively diagnosed disease (e.g. osteoarthritis) rather than symptoms (e.g. knee pain) were more likely to step up from weaker to stronger opioids (Foy et al., 2016). The median dose received by persistent analgesic users was significantly higher than that of non-persistent users across all studied analgesic classes.

Chapter 6 determined the proportion of patients with KOA who had a HES-linked record, and compared fall recording in both CPRD and HES-linked records. There were 365 patients (representing 15% of all recorded falls in the HES-linked population) who were identified as having an incident fall within HES records, but not in the CPRD. Subsequently, the HES-linked population was selected as the study population for further analyses on the association between analgesic use and the risk of falls.

Chapter 7 examined the association between analgesic use and the risk of falling among patients with KOA while adjusting for confounders, as identified from the literature. The study found that patients who used any analgesic within one year of their KOA diagnosis were at 89% higher risk of falling compared to those who did not use any analgesic. Reported HR

(95%CI) were 1.89 (1.66–2.16) adjusted for age, gender and use of fall risk increasing drugs (FRIDs).

Additionally, exposure to concomitant multiple analgesics was examined, and the risk of falling was proportional to the number of prescribed analgesics. Those using three analgesics were at more than three times the risk of falling compared to those not using any analgesic within one year of their KOA diagnosis, and HR (95%CI) was 3.24 (2.77, 3.78) adjusted for age, gender and use of FRIDs. The HRs (95%CI) for the risk of falling in those using two analgesic groups were between 2.45 (1.99–3.00) and 1.99 (1.71–2.31) compared to patients not using any analgesics.

Finally, Chapter 8 analysed the association between analgesic use and the risk of falling while treating analgesic prescriptions as a time-varying exposure. The findings were consistent with findings from the crude analyses and showed that the current use of analgesics was associated with a greater risk of falling compared to periods of no analgesic use. The reported HR (95%CI) were 1.46 (1.20, 1.78), 1.40 (0.91, 2.16), 2.40 (2.01, 2.85), 1.72 (1.43, 2.07) and 1.98 (1.68, 2.33) for antidepressants, AEDs, opioids, NSAIDs and paracetamol, respectively. The risk varied across the two six-monthly intervals of the first year following KOA diagnosis. During the first six months, the current use of opioids, NSAIDs and paracetamol was associated with a higher risk of falling than in the subsequent six months. Regarding antidepressants and AEDs, their current use was associated with a higher risk of falling during the second six-month interval. The striking finding within this chapter is that current paracetamol use was

associated with an increased risk of falling among the studied patients, with HR of 1.98 (95%CI 1.68, 2.33) during the first six months following KOA diagnosis, and 1.92 (95%CI 1.63, 2.26) during months seven to twelve following the diagnosis.

9.2 Methodological Approaches in the Thesis: Strengths and Limitations

The results from this thesis add to the body of knowledge on analgesic medicine use in the population of patients with KOA, as it has explored both medication use and its association with a clinically relevant outcome (falling). Having said that, these results must be interpreted with careful consideration of the strengths and limitations of the methodology and the analytical approaches applied in the studies.

A major strength of this research is that the dataset analysed was derived from the CPRD, a high-quality large primary care database in the UK. The use of CPRD as a source of patients' medical records provided a real-world dataset from which a nationally representative population of patients with KOA could be selected. The CPRD dataset was shown to be representative of the UK population as a whole, in terms of age, sex and socioeconomic status (Herrett et al., 2015). The use of CPRD therefore maximised the external validity of this research, so that conclusions on prescribing trends and patterns derived from present studies would be generalisable across the UK. Indeed, given the large number of included patients and the detailed

quantification of drug exposure at both population and patient levels, the results are possibly generalisable to all patients with KOA managed in primary care settings within other countries (with health systems similar to those of the UK, where, for example, management of KOA takes place in primary care).

The comprehensive records of prescribing enabled reliable analyses of exposure to medications to be based on using appropriate observational study, cross-sectional and cohort study designs. The cross-sectional design described the annual prescribing prevalence of the study drugs among primary care patients with KOA. Prevalence was estimated using the whole population of patients with KOA, and measured annually over a prolonged period (16 years). This minimised the possibility of obtaining differing results if another timeframe had been chosen (e.g. if only selected years were studied).

The cohort study design was applied to examine the association between analgesic use and the incidence of falling. Data was recorded prospectively, hence recall of medication exposures and falls was not a source of bias.

The utilisation of five separate drug classes was addressed in this research, including the analgesics recommended by national clinical guidelines such as NICE, namely paracetamol, NSAIDs and opioids. Additionally, the centrally acting drug classes commonly used in clinical practice for neuropathic pain management, namely antidepressants and AEDs, were included.

Typically, drug utilisation studies in patients with OA focus on opioids, non-opioids or both (Wright et al., 2014, Gore et al., 2012, Wilson et al., 2014). However, the present study included a wider range of drugs for OA pain, and hence, enabled assessing the changes over time in prescribing the first- and second-line analgesics (paracetamol, NSAIDs and opioids, respectively), in addition to other centrally acting KOA pain treatments (antidepressants and AEDs). The inclusion of multiple possible KOA pain drugs strengthened inferences on the association between analgesic use and the risk of falling.

Unlike many drug utilisation research studies (Wilson et al., 2014), this thesis included an analytical aspect of drug utilisation, and falling was selected as an outcome. Despite the lower prevalence of recorded falls in medical records compared to that reported in surveys (self-reported) (Gill et al., 2005), the use of EHR database is potentially the most reliable source for precise information for detailed drug exposure and confounder measurement. Prescription records in databases include complete information of the prescribed drugs, including the drug name, strength, dosage form and quantity prescribed. This enables the calculation of actual exposure over time, measured in calendar time (e.g. calendar years) or as patient time since first exposure (e.g. first patient year of treatment). Information on drug use obtained from alternative sources, such as patient interviews, is subjected to recall bias, leading to potential underestimation of drug exposure. Patients may choose to provide limited information, or

may choose to present selected containers of medications when asked to bring them all for review.

Data of the HES-linked-population was used to examine the association between medication use and the risk of falling within one year of KOA diagnosis. Although the proportion of patients who experienced a fall did not differ between the CPRD and HES databases, the HES-linked population included patients who had probably required escalated clinical care in a hospital setting (as opposed to primary care alone) as a consequence of a serious fall. The inclusion of patients with a fall identified in hospitalisation records implied the extent (seriousness) of consequences associated with exposure to drugs. It also strengthened the inferences from the study on the implications of drug use.

HES is a universal database that includes all patients treated in NHS hospitals, including private patients. HES codes were shown to have over 80% accuracy for administrative, diagnostic and medical intervention codes (NHS, March 2019).

Two separate analytical approaches investigated the association between analgesic medication use and the risk of falling. In the first approach, analgesic use was included as a time-fixed (time-invariant) exposure, while in the second approach, analgesic use was treated as a time-varying exposure. In both analyses, adjustments were made for potential confounders, including any previous fall (within one year before the date of KOA diagnosis), use of any FRIDs, and presence of any comorbidity.

In the crude analysis, the association was assessed by grouping analgesics whilst reflecting their stepwise application in OA-related pain management according to NICE (NICE, 2014b) and OARSI guidelines (McAlindon et al., 2014) . Additionally, the definition of exposure, as the prescription of multiple analgesics concomitantly, resembles real-life, where patients typically use more than one analgesic class during follow-up.

The time-varying analysis addressed a common and often overlooked source of bias in epidemiological studies, namely the immortal time bias. The immortal time bias can potentially overestimate the risk of the outcome, stemming from exposure misclassification (i.e. patients were classified as exposed when they are actually not). Findings from both analytical approaches enabled firmer conclusions to be drawn on the association between analgesic use and the risk of falling. Furthermore, the complementary application of a time-varying analysis demonstrated the value of applying more than one method to an epidemiological problem/question, and minimised potential bias in the estimates.

There were some limitations in this research, which need to be mentioned. There are no specific pharmacological treatments for KOA, meaning that identification of patients in EHR depends on diagnosis and problem coding (Yu et al., 2018). The diagnosis of KOA was based on Read and medical codes in CPRD records, where there may be the potential for misclassification bias from the use of routinely recorded and coded data. Knee osteoarthritis is a chronic condition characterised by knee joint pain and functional restriction, and therefore may possibly be coded based on

the presenting symptoms of knee pain, rather than KOA diagnosis, resulting in a potential underestimation. In fact, recording of the diagnosis of OA may be delayed for up to 7–10 years from the time of symptoms' appearance (Jordan et al., 2010), and the most common reason is the use of symptom-based codes. Another reason for under-recording of KOA in CPRD is the fact that recording depends on the presence of what are considered more important morbidities, e.g. MI or stroke. That is, OA is likely to be recorded if it is the primary complaint and in the absence of more acute diagnoses (Kadam et al., 2013). Furthermore, OA is not included in the Quality and Outcomes Framework (QOF); therefore, the quality and reliability of its routine recording may be suboptimal, potentially resulting in under-recording of OA diagnosis in the CPRD (Yu et al., 2017). In view of the above factors, which may lead to misclassification and under-recording of KOA, there was the potential for underestimation of the incidence of KOA among primary care patients in the UK.

The analysis was conducted on prescriptions generated in primary care, and assumptions were made that medications were dispensed and actually taken by patients. This may overestimate the actual drug utilisation, as research has shown that up to 50% of patients do not comply with their long-term therapies (Kisa et al., 2003).

Although the prescription records were comprehensive, OTC drugs are not recorded in the CPRD, resulting in incomplete records of all medications used. This may have led to an underestimation of drug exposure, as some of the studied analgesics are widely accessed by the public as OTC

products, including paracetamol and some NSAIDs (e.g. Ibuprofen 200mg and 400mg). However, most of the patients with KOA who were identified in this research were aged over 60 years old, thus qualifying for free prescriptions in the UK (NHS, 2017a), hence they are likely only to have a very small proportion of their analgesics not prescribed by GPs. Another source of possible exposure level underestimation is that drugs prescribed and dispensed in hospitals are not recorded in the CPRD. However, this is also not likely to form a major proportion of analgesic use, because OA/KOA is a chronic condition that is primarily managed in general practice in the UK.

The definition of persistent analgesic use applied in this study was adopted from studies on the persistence of opioids (Svendsen et al., 2012), and was not validated for other classes of analgesics. This might have led to a lack of specificity in the definition for analgesics other than opioids. However, in view of a lack of standardised definitions of persistent use of analgesics in the literature, the adopted definition was judged appropriate. The validity of the applied definition was confirmed by its ability to retain the cohort of persistent opioid users for three consecutive years (Svendsen et al., 2012); hence, it may be regarded as a valid tool for identifying the persistent pattern of drug use in population-based database studies.

The population included in the studies on the association between analgesic use and risk of falling were confined to English practices, as data from HES-linked practices were used. The final number of included patients dropped

by nearly 55% with the use of the HES-linked population. This may have potentially compromised the external validity of the research.

One of the limitations of the current research was related to the extent of patient-level data captured from the routinely collected database. Several variables, which may potentially have influenced the risk of falling, were not included in the analyses, and may represent a source of residual confounding. These mainly include covariates not captured in the routinely collected records, such as pain intensity, severity of comorbidities, and certain lifestyle measures (e.g. physical activity).

It was not possible to evaluate the effectiveness of pain management, nor was it possible to retrieve any of the pain scores on Visual Analogue Scales (VAS). Therefore, it was not known whether the prescribed analgesic regimens constituted an optimal pain management regimen for patients with KOA. The availability of information on the effectiveness of analgesia would inform clinical practice on the overall appropriateness of the prescribed regimens, including both effectiveness and safety. Such information would eventually aid decisions on the risk–benefit balance of prescribed analgesics.

Comorbidities included as confounders in investigating the association between analgesic use and the risk of falling were obtained from the QOF scheme, defined by Read codes. The scheme ensured that the recording of patients' long-term disease and health needs is both complete and accurate, through incentivising GP practices for the maintaining of accurate records

of patients. However, the QOF scheme was implemented from 2004 onwards, suggesting potentially underestimated quantification of QOF morbidities prior to 2004.

Another type of bias in observational studies is channelling bias, which results from the prescribing of specific analgesics according to the severity of the condition. It is likely that those in severe pain are prescribed multiple analgesics or stronger analgesics (e.g. opioids) than those prescribed to patients in less severe pain. However, the effect of channelling bias was minimised by investigating the association between analgesic use and the risk of falling within one year of KOA diagnosis, assuming that all patients will be at a similar level of pain severity when labelled with a diagnosis of KOA (Jordan et al., 2016).

Finally, a generalised ascertainment bias may have arisen from the fact that patients attending primary care consultations are more likely to report falls, or recall them when asked, than those not attending primary care consultations. Clinicians treating patients who are prescribed medications may be more conscious with regard to enquiring about falls in compliance with guidance. This would have possibly triggered better, complete recording of falls among this group of patients. This was probably the reason why fall recording overlapped between the CPRD and HES datasets (i.e. not many fall cases were found only in HES data without a record in CPRD, too), as found in Chapter 6 of this thesis.

9.3 Implications for Clinical Practice and Policy

Results obtained from this research have several implications that may be considered for possible implementation/adoption into practice.

9.3.1 Implications of Findings from Prescribing Prevalence

Findings from the prescribing trends suggest an overall increased prevalence of analgesic prescribing in patients with KOA, and indicate a need for regular monitoring. The successful management of KOA involves the integration of both non-pharmacological management (such as advice on exercise and weight loss support, and education on self-management) and medicines. Hence, it is important to ensure that core educational and lifestyle measures recommended by NICE are optimised when such an increase in the prevalence of analgesic prescribing is observed.

Previous research has shown that while GPs' attitudes and beliefs on the importance of exercise for chronic knee pain attributable to KOA were overall positive, only 11% of the GPs initiated exercise in alignment with best-evidence recommendations of the current quality standards on osteoarthritis (QS87) (NICE, 2015b) . The most commonly reported barriers were a lack of sufficient consultation time, reported by 51% of the 835 GPs; lack of expertise (training), reported by 41%; and the perception that patients prefer other management modalities, reported by 36% (Cottrell et al., 2017). These barriers and the subsequent limited uptake of core treatment (exercise and weight loss) and self-management measures may

in part explain the increasing prevalence of analgesic prescribing in primary care.

One of the strategies to ensure the provision of core treatments, recommended by NICE for patients with OA and enhanced care of patients with OA, is the application of innovations such as the model OA consultation (MOAC). The model consultation includes the OA guidebook, an enhanced consultation with a GP, and subsequent follow-up with a practice nurse in a dedicated OA clinic. These were applied in four GP practices within the UK in the context of a clinical trial. The intervention group received a MOAC, while the control group received the usual care (Dziedzic et al., 2018). Results showed a significantly higher uptake of core NICE recommendations after 6 months in the interventions arm than in the usual care control arm; for example, written exercise information provision increased by 20.5% (95% CI 7.9, 28.3) (Dziedzic et al., 2018). However, no evidence of the benefit of this intervention for physical functioning was found at six months. The mean difference in the 12-item Short Form Health Survey (SF-12) physical component summary (PCS) at the six-month primary end point was -0.37 (95%CI -2.32, 1.57). It was probably unrealistic to expect a change within the endpoint of six months for a long-term condition such as OA, and this may explain the lack of benefit of the intervention (Dziedzic et al., 2018).

Additionally, better uptake of OA guidelines on non-pharmacological management can be achieved through the introduction and application of electronic consultation templates in which OA management quality

indicators may be incorporated. The templates, triggered through OA or joint-specific OA code entry, include indicators such as assessment of pain and function, assessment for first-line analgesics, provision of information exercise, and weight loss advice (Edwards et al., 2015). Such a template may include alerts when second- or third-line analgesics are prescribed without optimal use of the non-pharmacological measures. Eventually, this may facilitate the optimised application of non-pharmacological management before or at the time of stepping up to the next level of prescription analgesics.

Importantly, the higher prevalence of opioid prescribing among patients with KOA compared to the other analgesic classes warrants special attention, particularly for those who fulfilled the criteria for persistent use within the first year following opioid initiation. These patients require regular review in clinical practice, as they are more vulnerable to problematic opioid use disorders, such as diversion, misuse and addiction. Similarly, those who used AEDs persistently (without epilepsy indications) warrant similar attention, being a group that is prone to problematic drug use (Evoy et al., 2017).

The higher prevalence of comorbidities among persistent analgesic users indicates the complex nature of these patients, as KOA-related pain is not a standalone condition. Hence, adequate interaction time with a GP needs to be allocated to ensure their health needs are addressed. The current standard consultation duration is set at 10 minutes, regardless of the patient's condition, with the average length of GP consultations in the UK

found to be 11.2 minutes, allowing the discussion of only 2.5 health problems (Salisbury et al., 2013), which seems inadequate to address the needs of patients with KOA who use single or multiple analgesic classes.

Optimised/longer consultation duration would also provide the opportunity for prescribers to review prior prescriptions and make decisions for further prescriptions, which may be needed to curtail the persistent use of opioids and gabapentinoids prescribed for patients with KOA.

9.3.2 Implications of Findings of the Association between Analgesic Use and the Risk of Falls

Evidence from this thesis suggests that the studied classes of analgesics were associated with an increased risk of falls in patients with KOA. This implies that a careful evaluation of benefits and adverse outcomes is required when prescribing, which should include the tailoring of drugs to individual patients.

This risk of falling was associated with exposure to antidepressants, including the “other antidepressants” subclass. This may have an implication for practice, where SNRIs are generally regarded as safer antidepressants (Vestergaard et al., 2008) than SSRIs due to fewer drug–drug interactions. Clinicians need to be alert to this finding, since the use of another antidepressant subclass was not found to show reduced incidence of adverse outcomes, such as falls, compared to TCA and SRRI subclasses (Coupland et al., 2011). Although this finding was revealed in a large cohort study on the safety of antidepressants in primary care patients with

depression, it is still relevant to patients with KOA, who are likely to constitute a subgroup among those who are diagnosed with depression.

There was evidence from the present study that the combination/concomitant use of more than one of the studied analgesic classes was associated with an increased risk of falling. Although the use of multiple analgesic classes may reflect increased severity of pain and a lack of adequate response to a single class, it is a matter of concern that warrants prioritised attention from clinical teams.

Patients with KOA who use multiple analgesic classes need to be identified as a vulnerable group of patients with increased risk of falling, and this provides an opportunity to intervene early through the delivery of multifactorial interventions, hence reducing the personal and societal costs of falls. Multifactorial programmes include health education and home hazards environmental evaluation/modification, along with medication review and ophthalmology consultations (Lee et al., 2013).

In the UK, guidelines on the identification of people at risk of falling are in place; however, suboptimal referral to specialist services has been an issue (Jonathan Treml, 2011).

The NICE guidelines on the prevention of falls, and their quality standards, recommend that older people in contact with health care providers are routinely asked about their fall history over the past year. The guidelines also highlight the critical role of health care providers in primary care in identifying those who are at risk of falling, and referring them to specialised

fall-prevention services (NICE, 2015b). According to NICE quality standards, people at risk who require referral to a falls service include all those who have received medical attention for a fall, or have fallen more than once in a year.

However, the number of patients who are actually referred to specialist fall services is far less than the number expected, and there has been a recommendation for an urgent upscaling of the capacity of fall clinics by as much as ten-fold to meet the needs of the population of older fallers (Jonathan Treml, 2011). At a national level, low referral to fall-prevention services mean that there are thousands of missed opportunities for intervention to prevent falls.

One way to optimise referral to fall clinics is to regard patients with KOA as a group with a priority for referral, particularly those who are prescribed analgesics.

The study also found that the risk of falling was higher with the current use of any analgesic during the first year following KOA diagnosis; however, this varied across analgesic classes and within the two six-monthly time intervals. This implies that patients are at a greater risk of falling when they use analgesics, particularly when initiating treatments.

Regarding antidepressants and AEDs, current use was associated with a higher risk of falling during the second six-month interval. Again, this has important implications, as those patients currently using antidepressants

and AEDs need to remain vigilant for fall risk during periods of use, regardless of when they were first prescribed.

Prescribers as well as patients need to be aware of such information and follow appropriate measures, such as restricting (if appropriate) new prescriptions of any additional treatments which may increase the risk of falling.

The striking finding in this study is that current paracetamol use was associated with an increased risk of falling among the studied patients, which forms an additional call for routine close patient reviews to ensure the safety of patients who are prescribed any analgesic, even those regarded as safe options (e.g. paracetamol).

Taken together, the above points support the notion that patients with KOA require an integrated care model targeting their KOA-related pain, and also considering their multiple health needs. Such a model of care promotes the involvement of multidisciplinary providers in patients' routine primary care in order to deliver care with a holistic approach. This also involves the preparation of care plans, agreed between patients and health care providers.

One of the key roles within the multidisciplinary team is that of medicines management pharmacists within the primary care team managing patients with KOA. The focus of a pharmacy professional would be to conduct medication reviews (or review those conducted by prescribers), advise on withdrawal of unrequired drugs (de-prescribing), or suggest safer

substitutions. For example, FRIDs including benzodiazepines were frequently prescribed for the study cohort, probably for conditions such as anxiety with chronic pain. However, there are significant risks associated with such prescribing, and evidence showed that the history of benzodiazepine prescription and current prescription are both associated with an increased risk of death among opioid users (Park et al., 2015).

Moreover, recent studies have also concluded the higher risk of opioid-related fatalities among patients who use gabapentinoids with opioids concomitantly (Gomes et al., 2018, Gomes et al., 2017). With the increase in the prescribing prevalence of newer AEDs, particularly gabapentinoids, in this study, great emphasis must be placed on education to raise awareness through information campaigns, and training of practitioners and patients on the risks associated with their use, especially when used concomitantly with opioids. The insufficiency of evidence of opioid effectiveness for long-term use or in high doses needs to be highlighted to patients during reviews.

The potential problem of dose escalation cycles in persistent users of opioids and gabapentinoids requires attention. That is, higher doses may be prescribed to maximise analgesia, which may result in tolerance, and subsequently may lead to further dose escalation, resulting in a vicious dose escalation cycle. In Norway, 68% of persistent opioid users continued the same pattern for the following two years (n=45,950) (Svendsen et al., 2012). In the UK, the work by Bedson et al. (2016) showed that 28.6% of those who started a long-term episode of opioid use (n=76,416) remained in the

same episode for the following two years, and that 22.6% used potent, controlled, long-acting preparations (Bedson et al., 2016). A separate study in Canada showed that among those receiving chronic opioid therapy (≥ 3 months or more), 1.8% of cases escalated to high doses (i.e. >200mg morphine or equivalent per day), within a median follow-up of 186 days (IQR 117 to 442) (Kaplovitch et al., 2015). Taken together, this evidence suggests the likelihood of proportion of persistent opioid users having their dosage escalate.

There is, therefore, a need for careful selection of patients prior to opioid and gabapentinoid initiation, with consideration of unwarranted dose escalations and drug–drug interactions.

Given the importance of managing analgesics in these patients, and the consequences associated with their use, osteoarthritis quality standards (NICE, 2015b) need to include a statement of this fundamental issue to ensure adequate attention is being paid to analgesic use, including their persistent and concomitant uses.

Finally, an online resource on osteoarthritis that captures resources – including guidelines, quality standards, prescribing information, MOAC contents and electronic templates – under one platform will both educate professionals and inform patient care. An example of such a comprehensive resource is “Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines in pain”. The

resource was collated by the Faculty of Pain Medicine, with several stakeholders, including NICE and Public Health England (FPM, 2019b).

9.4 Implications for Research

Future research needs to confirm the findings from this work, and examine the association between drug use and the risk of falling over longer periods of follow-up. This is of great importance, as the present work has identified the risk of falling with current use of paracetamol, the universal first-line analgesic in KOA management. Simultaneously, the effect of various dose levels or extent of exposure associated with increased risks of adverse outcomes in patients with OA in general, and with KOA specifically, needs to be determined.

Additionally, further studies are required to develop risk prediction models to individualise the risk of falling and other adverse outcomes associated with analgesic use, so that the patients facing the highest risks are identified and monitored closely. These models may be based on criteria such as patients' comorbidities; previous fall history; use of analgesics, specifically opioids, gabapentinoids and antidepressants; and the total number of analgesics used concomitantly.

Currently, there is much literature describing the traits of patients who are likely to develop long-term use and persistent use patterns of opioids (Krebs et al., 2010, Oh et al., 2019). However, the traits of patients persistently using the other analgesic classes, particularly dependence-forming

substances (e.g. gabapentinoids), are less well described. Furthermore, the proportion and traits of those using more than one class, namely opioids and gabapentinoids concomitantly, need to be determined.

Additionally, future research needs to clarify the steps and approaches for stepping down the persistent use of these dependence-forming substances. Recently, Foy et al. (2016) suggested that patients with multi-morbidity and polypharmacy represent the most obvious and pressing target for de-prescribing opioids. However, no further details were suggested regarding the specific patient groups to target, e.g. those diagnosed with KOA and prescribed dependence-forming drug classes (Foy et al., 2016).

One of the key future research areas is the optimisation of methods for time-varying exposure, which needs to be further developed to capture the use of multiple drugs, and when these are used concomitantly, as this is common in patients with KOA. The wider use of time-varying analyses will ensure minimised immortal time bias, which is an acknowledged limitation in observational studies, particularly those on the effectiveness or safety of drug use (Suissa et al., 2002).

Randomised clinical trials of analgesics in patients with OA or KOA in primary care settings, with sufficient length of follow-up and size, are lacking (Losina et al., 2013). There is a need for long-term randomised trials to assess a range of adverse outcomes (e.g. all-cause mortality, sudden cardiac death, fractures), and compare benefits and risks across analgesic classes and with different patterns of use (e.g. persistent use vs non-

persistent use). This will provide high-quality evidence to inform public health, optimal practice and policy, and the safe use of analgesics.

Further research may also be conducted to estimate the loss in utility associated with each adverse outcome. This would then be used to calculate the quality-adjusted life years (QALY) loss associated with different types of analgesic, and patterns of use for each adverse outcome.

Future qualitative studies are much needed to understand patient experiences of persistent use of analgesics both generally and with opioids, gabapentinoids specifically, in terms of achieving adequate pain control and incidence of adverse outcomes. Qualitative research is also required to gain greater insight into patients' trajectories to persistent and concomitant use of analgesics. A summary of all implications is included in Figure 1.

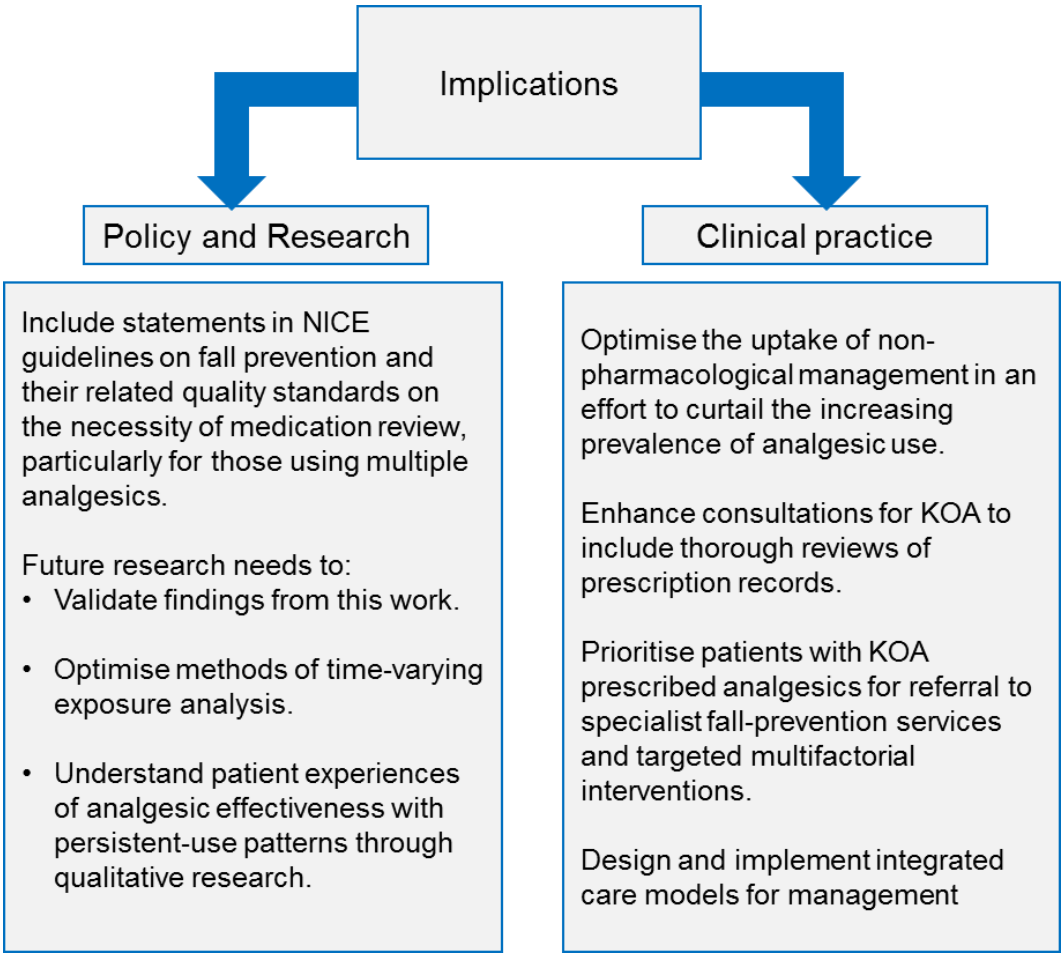


Figure 9-1 Summary of the Research Implications.

9.5 Conclusion

This study selected a cohort of patients with KOA from CPRD data, and estimated the annual incidence of diagnosed KOA in UK primary care settings between 2000 and 2015. The study described the utilisation of antidepressants, AEDs, opioids, NSAIDs and paracetamol over a period of 16 years in a cohort of primary care patients with KOA. An overall increase in drug utilisation measures was observed through most of the study years, and opioid prescribing was most prevalent. Variable proportions of patients used the studied analgesic drugs persistently within one year following the first prescription.

The association between analgesic use and the risk of falling was investigated, and patients using any analgesic were at 89% higher risk of falling within the first year following KOA diagnosis. The risk of falling was significantly higher during periods of current analgesic use compared to periods of no analgesic use.

Knee osteoarthritis needs to be acknowledged as a public health priority in the UK and Europe. Efforts need to be directed towards its prevention, better implementation of non-pharmacological management, and focused attention on analgesic management in this group of patients. This includes assessing, monitoring and mitigating the risk of falling, a serious outcome associated with analgesic use.

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Appendix 1 ISAC Protocol

Appendix 1 Table I.I – ISAC protocol

ISAC APPLICATION FORM PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

For ISAC use only		
Protocol No. Submission date (DD/MM/YYYY)	18_170R 25/06/2018	**IMPORTANT** Please refer to the **guidance** for '**Completing the ISAC application form'** found on the CPRD website (www.cprd.com/isac). If you have any queries, please contact the ISAC Secretariat at isac@cprd.com.

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY
1. Study Title§ (Please state the study title below) Drug utilisation among primary care patients with knee osteoarthritis (KOA): a population-based study using CPRD §Please note: This information will be published on the CPRD's website as part of its transparency policy.
2. Has any part of this research proposal or a related proposal been previously submitted to ISAC? Yes * ☐ No ☒ *If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.
3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee) Yes* ☐ No ☒ *If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	☒	Pharmacoeconomics	☐
Disease Epidemiology	☐	Post-authorisation Safety	☐
Health care resource utilisation	☐	Methodological Research	☐
Health/Public Health Services Research	☐	Other*	☐

*If Other, please specify the type of study here and in the lay summary below:

5. Health Outcomes to be Measured§

§Please note: This information will be published on CPRD's website as part of its transparency policy.

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

1. Prevalence and trends of analgesic prescribing in patients with KOA
2. Risk of falls in patients with KOA.
3. Risk of all-ca mortality in pati with KOA

[Please add more bullet points as necessary]

6. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☐	Regulatory purposes	☐
Other*	☐		

*If Other, please provide further information:

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

7. Chief Investigator§

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Dr Roger Knaggs

Associate Professor in Clinical Pharmacy Practice

School of Pharmacy | University of Nottingham

E-mail: roger.knaggs@nottingham.ac.uk

Specialist Pharmacist in Pain Management
Primary Integrated Community Solutions | Unit H4 Ash Tree Court |
Nottingham Business Park | Nottingham | NG8 6PY | United Kingdom
Tel: +44 (0)115 8834172 | E-mail: roger.knaggs@nhs.net

§Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy

CV has been previously submitted to ISAC	☒	**CV number:**	131_17
A new CV is being submitted with this protocol	☐		
An updated CV is being submitted with this protocol	☐		

8. Affiliation of Chief Investigator (full address)

Associate Professor in Clinical Pharmacy Practice

School of Pharmacy | University of Nottingham |Nottingham | NG7 2RD | United Kingdom

Tel: +44 (0)115 846 6382 (Internal 66382) | Fax: +44 (0)115 846 6249

E-mail: roger.knaggs@nottingham.ac.uk

Specialist Pharmacist in Pain Management
Primary Integrated Community Solutions | Unit H4 Ash Tree Court |
Nottingham Business Park | Nottingham | NG8 6PY | United Kingdom
Tel: +44 (0)115 8834172 | E-mail: roger.knaggs@nhs.net

9. Corresponding Applicant§
Please state the full name, affiliation(s) and e-mail address below:

Aqila Mohammed Hassan Taqi

University of Nottingham

School of Pharmacy

Division of Pharmacy Practice and Policy

University Park

NG7 2RD

Nottingham

Email: paxat4@nottingham.ac.uk

§Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy

Same as chief investigator ☐

CV has been previously submitted to ISAC ☐ **CV number:**

A new CV is being submitted with this protocol ☒

An updated CV is being submitted with this protocol ☐

10. List of all investigators/collaborators§
Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

§Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy

Other investigator:

Dr Harmony Otete

Lecturer in Medical Statistics School of Medicine, UCLAN, Harrington Building 242, Preston PR1 2HE.

hotete@uclan.ac.uk

CV has been previously submitted to ISAC ☒ **CV number:** 501_16ES

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Dr. Sonia Ratib

Assistant Professor

Faculty of Medicine & Health Sciences

Centre of Evidence Based Dermatology | King's Meadow Campus

Lenton Lane| Nottingham | NG7 2NR

Tel: 0115 7286370

Sonia.Ratib@nottingham.ac.uk

CV has been previously submitted to ISAC ☒ **CV number:** 269_16ES

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

*Please note that your ISAC application form and protocol **must** be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.

11. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work

*Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.

Dr Knaggs has nothing to disclose Dr. Otete has nothing to disclose, Dr. Ratib has nothing to disclose and Mrs Taqi has nothing to disclose.

12. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	**Publications using GPRD/CPRD data**
None	☐	☐
1-3	☐	☐
> 3	☒	☒

Experience/Expertise available	Yes	No
Is statistical expertise available within the research team? If yes, please indicate the name(s) of the relevant investigator(s) Dr Harmony Otete has been trained in pharmacoepidemiology and Dr Sonia Ratib is a medical statistician, both can provide statistical expertise in longitudinal data analysis of this project.	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? If yes, please indicate the name(s) of the relevant investigator(s) Dr. Roger Knaggs, Dr. Harmony Otete and Dr. Sonia Ratib are experienced in extraction and data management of large data sets.	☒	☐
Is experience of practising in UK primary care available to or within the research team? If yes, please indicate the name(s) of the relevant investigator(s) Dr.Roger Knaggs has many years' experience as a practising consultant pharmacist in the area of pain management. He also has extensive experience of undertaking research in UK primary care and pain management services, including studies involving analysis of large datasets extracted from UK general practices.	☒	☐

13. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

1. Zin, C., Chen, L.-C., & Knaggs, R. (2014). Changes in trends and pattern of strong opioid prescribing in primary care. European Journal of Pain (London, England), 18(9), 1343–1351.

2. Svendsen, K., Skurtveit, S., Romundstad, P., Borchgrevink, P.C. and Fredheim, O.M.S. (2012), Differential patterns of opioid use: Defining persistent opioid use in a prescription database. EJP, 16: 359–369.

3. Coupland, C., Dhiman, P., Morriss, R., Arthur, A., Barton, G., & Hippisley-Cox, J. (2011). Antidepressant use and risk of adverse outcomes in older people: population based cohort study. The BMJ, 343, d4551.

SECTION C: ACCESS TO THE DATA

1. **Financial Sponsor of study**[§]

[§]Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy

Pharmaceutical Industry	☐	Please specify name and country:
Academia UK	☒	Please specify name and country: : University of Nottingham,
Government / NHS	☐	Please specify name and country:
Charity	☐	Please specify name and country:
Other	☐	Please specify name and country:
None	☐	

2. **Type of Institution conducting the research**

Pharmaceutical Industry	☐	Please specify name and country:
Academia UK	☒	Please specify name and country: University of Nottingham,
Government Department	☐	Please specify name and country:
Research Service Provider	☐	Please specify name and country:
NHS	☐	Please specify name and country:
Other	☐	Please specify name and country:

3. **Data access arrangements**

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data	☐
The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data**	☒
A data set will be provided by the CPRD[¥€]	☐
CPRD has been commissioned to extract the data and perform the analyses[€]	☐
Other:	☐

If Other, please specify:

*Collaborators supplying data for this study must be named on the protocol as co-applicants.

**If data sources other than CPRD GOLD are required, these will be supplied by CPRD

[¥]Please note that datasets provided by CPRD are limited in size; applicants should contact CPRD (enquiries@cprd.com) if a dataset of >300,000 patients is required.

€Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):

Name of CPRD Researcher	Reference number (where available)	Date of contact

4. **Primary care data**

Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐

EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.

*Investigators requiring the use of EMIS data **must** discuss the study with a member of the CPRD Research team before submitting an ISAC application

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:

Name of CPRD Researcher	Reference number (where available)	Date of contact

SECTION D: INFORMATION ON DATA LINKAGES

5. Does this protocol seek access to linked data

Yes* ☒ No☐ If No, please move to section E.

*Research groups which have not previously accessed CPRD linked data resources **must** discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset, PROMS data, the Pregnancy Register, Cancer Registration, SACT and CPES data and the Mental Health Services Data Set **must** also discuss this with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email enquiries@cprd.comto discuss your requirements **before** submitting your application.

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

Name of CPRD Researcher Taita Murrary-Thomas (Tarita.Murray-Thomas@mhra.gsi.gov.uk)

Reference number (where available) CPRD00023118 Date of contact 8/5/2018

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

6. Please select the source(s) of linked data being requested[§]

[§]Please note: This information will be published on the CPRD's website as part of its transparency policy.

☒ ONS Death Registration Data

☒ HES Admitted Patient Care

☐ HES Outpatient

☐ HES Accident and Emergency

☐ HES Diagnostic Imaging Dataset ☐ HES PROMS (Patient Reported Outcomes Measure)**

☐ CPRD Mother Baby Link

☐ Pregnancy Register

☐ MINAP (Myocardial Ischaemia National Audit Project)

☐ NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data *

☐ NCRAS Cancer Patient Experience Survey (CPES) data*

☐ NCRAS Systemic Anti-Cancer Treatment (SACT) data*

☐ Mental Health Services Data Set (MHDS)

☐ Practice Level Index of Multiple Deprivation (Standard)

☐ Practice Level Index of Multiple Deprivation (Bespoke)

☒ Patient Level Index of Multiple Deprivation***

☐ Patient Level Townsend Score ***

☐ Other**** Please specify:

*Applicants seeking access to NCRAS data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website.

**Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only accessible by academics

*** 'Patient level IMD and Townsend scores will not be supplied for the same study

****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.

Name of CPRD Researcher | Reference number (where available) | Date of contact

7. **Total number of linked datasets requested <u>including</u> CPRD GOLD**

Number of linked datasets requested (practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **not** be included in this count) 3

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

8. Is linkage to a local¥ dataset with <1 million patients being requested?

Yes * ☐ No ☒

*If yes, please provide further details:

¥ Data from defined geographical areas i.e. non-national datasets.

9. **If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.**

Yes* ☐ No ☒

* If yes, please provide further details:

10. Does this study involve linking to patient identifiable data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

11. Does this protocol describe a purely observational study using CPRD data?

Yes* ☒ No** ☐

* Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.

** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.

12. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

* If yes, please indicate what will be required:

Completion of questionnaires by the GP□ Yes ☐ No ☐

Is the questionnaire a validated instrument? Yes ☐ No ☐

If yes, has permission been obtained to use the instrument? Yes ☐ No ☐

Please provide further information:

Other (please describe)

□ Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

13. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No ☒

*Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.

14. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

* Please state what will be collected:

SECTION F: DECLARATION

15. Signature from the Chief Investigator

- I have read the guidance on '**Completion of the ISAC application form**' and '**Contents of CPRD ISAC Research Protocols**' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.

- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Roger Knaggs Date: 25th June 2018 e-Signature (type name):

Appendix 1 Table 1.2 – Read Codes for Osteoarthritis

Read Code	Code Description
N054900	Oligoarticular osteoarthritis; unspecified; multiple sites
N054800	Oligoarticular osteoarthritis; unspecified; other spec sites
N054700	Oligoarticular osteoarthritis; unspecified; of ankle/foot
N054600	Oligoarticular osteoarthritis; unspecified; of lower leg
N054500	Oligoarticular osteoarthritis; unspecified; of pelvis/thigh
N054400	Oligoarticular osteoarthritis; unspecified; of hand
N054200	Oligoarticular osteoarthritis; unspecified; of upper arm
N054100	Oligoarticular osteoarthritis; unspecified; of shoulder
N054000	Oligoarticular osteoarthritis; unspec; of unspecified sites
N053800	Localised osteoarthritis; unspecified; of other spec site
N053700	Localised osteoarthritis; unspecified; of the ankle and foot
N053611	Patellofemoral osteoarthritis
N053600	Localised osteoarthritis; unspecified; of the lower leg
N053500	Localised osteoarthritis; unspecified; pelvic region/thigh
N053400	Localised osteoarthritis; unspecified; of the hand
N053300	Localised osteoarthritis; unspecified; of the forearm
N053200	Localised osteoarthritis; unspecified; of the upper arm
N053100	Localised osteoarthritis; unspecified; of shoulder region
N053000	Localised osteoarthritis; unspecified; of unspecified site
N052800	Localised; secondary osteoarthritis of other specified site
N052700	Localised; secondary osteoarthritis of the ankle and foot
N052600	Localised; secondary osteoarthritis of the lower leg
N052500	Localised; secondary osteoarthritis of pelvic region/thigh
N052400	Localised; secondary osteoarthritis of the hand
N052300	Localised; secondary osteoarthritis of the forearm
N052200	Localised; secondary osteoarthritis of the upper arm
N052100	Localised; secondary osteoarthritis of the shoulder region
N052000	Localised; secondary osteoarthritis of unspecified site
N051800	Localised; primary osteoarthritis of other specified site
N051700	Localised; primary osteoarthritis of the ankle and foot
N051600	Localised; primary osteoarthritis of the lower leg
N051500	Localised; primary osteoarthritis of the pelvic region/thigh
N051400	Localised; primary osteoarthritis of the hand
N051300	Localised; primary osteoarthritis of the forearm
N051200	Localised; primary osteoarthritis of the upper arm
N051100	Localised; primary osteoarthritis of the shoulder region
N051000	Localised; primary osteoarthritis of unspecified site
N050600	Erosive osteoarthrosis
N050400	Primary generalized osteoarthrosis
N050200	Generalised osteoarthritis of multiple sites
N050100	Generalised osteoarthritis of the hand
N050000	Generalised osteoarthritis of unspecified site
N110.12	Osteoarthritis cervical spine
N054z00	Osteoarthritis of more than one site; unspecified; NOS
N054.00	Oligoarticular osteoarthritis; unspecified
N053z00	Localised osteoarthritis; unspecified; NOS
N053.00	Localised osteoarthritis; unspecified
N052z00	Localised; secondary osteoarthritis NOS
N052.00	Localised; secondary osteoarthritis
N051z00	Localised; primary osteoarthritis NOS
N051F00	Localised; primary osteoarthritis of elbow
N051E00	Localised; primary osteoarthritis of toe

Read Code	Code Description
N051D00	Localised; primary osteoarthritis of the wrist
N051.00	Localised; primary osteoarthritis
N050z00	Generalised osteoarthritis NOS
N050.00	Generalised osteoarthritis - OA
N11z.11	Osteoarthritis spine
N11D.00	Osteoarthritis of spine
N11D300	Osteoarthritis of spine NOS
N11D200	Osteoarthritis of lumbar spine
N11D100	Osteoarthritis of thoracic spine
N11D000	Osteoarthritis of cervical spine
N11..12	Osteoarthritis of spine
N05zz00	Osteoarthritis NOS
N05zU00	Osteoarthritis NOS; of IP joint of toe
N05zT00	Osteoarthritis NOS; of lesser MTP joint
N05zS00	Osteoarthritis NOS; of 1st MTP joint
N05zR00	Osteoarthritis NOS; of other tarsal joint
N05zQ00	Osteoarthritis NOS; of talonavicular joint
N05zP00	Osteoarthritis NOS; of subtalar joint
N05zN00	Osteoarthritis NOS; of ankle
N05zM00	Osteoarthritis NOS; of tibio-fibular joint
N05zL00	Osteoarthritis NOS; of knee
N05zK00	Osteoarthritis NOS; of sacro-iliac joint
N05zJ00	Osteoarthritis NOS; of hip
N05zH00	Osteoarthritis NOS; of DIP joint of finger
N05zG00	Osteoarthritis NOS; of PIP joint of finger
N05zF00	Osteoarthritis NOS; of MCP joint
N05zE00	Osteoarthritis NOS; of wrist
N05zD00	Osteoarthritis NOS; of distal radio-ulnar joint
N05zC00	Osteoarthritis NOS; of elbow
N05zB00	Osteoarthritis NOS; of acromioclavicular joint
N05zA00	Osteoarthritis NOS; of sternoclavicular joint
N05z.00	Osteoarthritis NOS
N05z900	Osteoarthritis NOS; of shoulder
N05z800	Osteoarthritis NOS; other specified site
N05z713	Toe osteoarthritis NOS
N05z712	Foot osteoarthritis NOS
N05z711	Ankle osteoarthritis NOS
N05z700	Osteoarthritis NOS; of ankle and foot
N05z611	Knee osteoarthritis NOS
N05z600	Osteoarthritis NOS; of the lower leg
N05z511	Hip osteoarthritis NOS
N05z500	Osteoarthritis NOS; pelvic region/thigh
N05z412	Thumb osteoarthritis NOS
N05z411	Finger osteoarthritis NOS
N05z400	Osteoarthritis NOS; of the hand
N05z311	Wrist osteoarthritis NOS
N05z300	Osteoarthritis NOS; of the forearm
N05z211	Elbow osteoarthritis NOS
N05z200	Osteoarthritis NOS; of the upper arm
N05z100	Osteoarthritis NOS; of shoulder region
N05z000	Osteoarthritis NOS; of unspecified site
N05..11	Osteoarthritis
N05..00	Osteoarthritis and allied disorders
7131DL	Lumbar osteoarthritis

Read Code	Code Description
7131C	Osteoarthrosis spine
7131BR	Spondylitis Osteoarthritic
7131A	Osteoarthrosis neck
7130PA	Osteoarthritic protrusion acetabulum
7130N	Osteoarthrosis hands
7130MD	Temporomandibular osteoarthrosis
7130H	Osteoarthrosis toe
7130FT	Osteoarthrosis foot
7130EL	Osteoarthrosis elbow
7130EA	Sternoclavicular joint osteoarthrosis
7130E	Osteoarthrosis shoulder
7130DA	Osteoarthritis hip
7130D	Osteoarthrosis hip
7130CT	Thumb osteoarthrosis
7130C	Osteoarthrosis fingers
7130B	Osteoarthrosis knee(s)
7130AW	Osteoarthrosis wrist
7130AG	Osteoarthrosis general
7130AC	Osteoarthrosis acromio clavicular joint
7130AB	Osteoarthrosis
7130AA	Osteoarthrosis ankle
7130A	Osteoarthritis
Knee pain symptoms codes	
Read codes	**Description**
1M10	Knee pain
1M12	Anterior knee pain
N094M	Arthralgia of knee
N094W	Anterior knee pain
N0946	Knee joint pain
N2431	Hypertrophy of knee fat pad
N0906	Knee joint effusion
N090M	Effusion of knee
N092M	Villonodular synovitis of knee
N0956	Knee stiff
N095M	Stiff knee NEC
N0966	Knee gives way
N096M	Other symptoms - knee
N098B	Synov osteochondromat-knee
N099C	Clicking knee
N2160	Bursitis of knee NOS
N2162	Tibial collateral lig.bursitis
N2163	Fibular collat.lig.bursitis
N2164	Patellar tendinitis
N2165	Prepatellar bursitis
N2166	Infrapatellar bursitis
N2167	Subpatellar bursitis
N216z	Suprapatellar bursitis
N220z	Synovitis of knee
N3640	Knock knee

Knee osteoarthritis diagnosis codes applied in cohort selection		
Possible knee osteoarthritis codes		
21159	N05z600	Osteoarthritis NOS;of the lower leg
33479	N054600	Oligoarticular osteoarthritis; unspecified; of lower leg
34804	N051600	Localised; primary osteoarthritis of the lower leg
24079	Nyu2511	Primary gonarthrosis
24145	Nyu2811	Seconadary gonarthrosis
24146	N051B00	Primary gonarthrosis, bilateral
Three definite knee osteoarthritis codes		
665	N05z611	Knee osteoarthritis NOS
1296	N053611	Patellofemoral osteoarthritis
2487	N05zL00	Osteoarthritis NOS, of knee
Two definite knee osteoarthritis codes		
665	N05z611	Knee osteoarthritis NOS
2487	N05zL00	Osteoarthritis NOS; of knee

Appendix 1 Table 1.3 - Cancer and Rheumatoid Arthritis Medcodes

Read Code	Term
Cancer	
B210.00	Malignant neoplasm of glottis
B21..00	Malignant neoplasm of larynx
B49..00	Malignant neoplasm of urinary bladder
B46..00	Malignant neoplasm of prostate
B32..00	Malignant melanoma of skin
B5z..00	Malignant neoplasm of other and unspecified site NOS
B10..00	Malignant neoplasm of oesophagus
B13..00	Malignant neoplasm of colon
B4A0.00	Malignant neoplasm of kidney parenchyma
B141.00	Malignant neoplasm of rectum
B580.00	Secondary malignant neoplasm of kidney
B440.11	Cancer of ovary
B33z.00	Malignant neoplasm of skin NOS
B22z.11	Lung cancer
B40..00	Malignant neoplasm of uterus, part unspecified
B40..00	Malignant neoplasm of uterus, part unspecified
B41..00	Malignant neoplasm of cervix uteri
B....11	Cancers
B133.00	Malignant neoplasm of sigmoid colon
B430200	Malignant neoplasm of endometrium of corpus uteri
B430.00	Malignant neoplasm of corpus uteri, excluding isthmus
B48..00	Malignant neoplasm of penis and other male genital organs
B134.00	Malignant neoplasm of caecum
B22z.00	Malignant neoplasm of bronchus or lung NOS
B34..00	Malignant neoplasm of female breast
PE1..12	Sternomastoid tumour
B541.00	Malignant neoplasm of parathyroid gland
B020.00	Malignant neoplasm of parotid gland
B454.00	Malignant neoplasm of vulva unspecified
B33..00	Other malignant neoplasm of skin
B10z.11	Oesophageal cancer
B900011	Mixed parotid tumour
B583000	Secondary malignant neoplasm of brain
F122.00	Malignant neuroleptic syndrome
B53..00	Malignant neoplasm of thyroid gland
B58..00	Secondary malignant neoplasm of other specified sites
BB06.00	[M]Tumour cells, uncertain whether benign or malignant
BBC3.00	[M]Granulosa cell tumour NOS
B12..00	Malignant neoplasm of small intestine and duodenum
BB05.00	[M]Tumour cells, benign
B131.00	Malignant neoplasm of transverse colon
B43..00	Malignant neoplasm of body of uterus
H51y700	Malignant pleural effusion
B585.00	Secondary malignant neoplasm of bone and bone marrow
B440.00	Malignant neoplasm of ovary
B161200	Malignant neoplasm of common bile duct
B576200	Malignant ascites
B17..00	Malignant neoplasm of pancreas
B11..00	Malignant neoplasm of stomach
B542000	Malignant neoplasm of pituitary gland
BB07.00	[M]Tumour cells, malignant

B170.00	Malignant neoplasm of head of pancreas
B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
B55..00	Malignant neoplasm of other and ill-defined sites
B130.00	Malignant neoplasm of hepatic flexure of colon
B21z.00	Malignant neoplasm of larynx NOS
1J09.00	Suspected bladder cancer
B34z.00	Malignant neoplasm of female breast NOS
B582600	Secondary malignant neoplasm of skin of breast
B56..00	Secondary and unspecified malignant neoplasm of lymph nodes
B525.00	Malignant neoplasm of cauda equina
B01..00	Malignant neoplasm of tongue
B222.00	Malignant neoplasm of upper lobe, bronchus or lung
B450100	Malignant neoplasm of vaginal vault
BB10.00	[M]Epithelial tumour, benign
B51..11	Cerebral tumour - malignant
B132.00	Malignant neoplasm of descending colon
1J03.00	Suspected brain tumour
B136.00	Malignant neoplasm of ascending colon
B162.00	Malignant neoplasm of ampulla of Vater
B5...00	Malignant neoplasm of other and unspecified sites
B593.00	Primary malignant neoplasm of unknown site
B702300	Warthin's tumour
B1z0.11	Cancer of bowel
BBCG.00	[M]Sclerosing stromal tumour
B454.11	Primary vulval cancer
B6...00	Malignant neoplasm of lymphatic and haemopoietic tissue
B62y.00	Malignant lymphoma NOS
B4A1.00	Malignant neoplasm of renal pelvis
B550200	Malignant neoplasm of nose NOS
Byu6.00	[X]Malignant neoplasm of breast
B224100	Malignant neoplasm of lower lobe of lung
B221.00	Malignant neoplasm of main bronchus
B22..00	Malignant neoplasm of trachea, bronchus and lung
B4...00	Malignant neoplasm of genitourinary organ
1J00.00	Suspected lung cancer
B00..00	Malignant neoplasm of lip
B05..00	Malignant neoplasm of other and unspecified parts of mouth
B11z.00	Malignant neoplasm of stomach NOS
B62yz00	Malignant lymphoma NOS
B626.00	Malignant mast cell tumours
B577.00	Secondary malignant neoplasm of liver
B47..00	Malignant neoplasm of testis
B7J0.11	Glomus tumour
B31z.00	Malignant neoplasm of connective and soft tissue, site NOS
B220.00	Malignant neoplasm of trachea
B4A2.00	Malignant neoplasm of ureter
G200.00	Malignant essential hypertension
B62y800	Malignant lymphoma NOS of lymph nodes of multiple sites
BB01.00	[M]Neoplasm, uncertain whether benign or malignant
B4A3.00	Malignant neoplasm of urethra
B204.00	Malignant neoplasm of frontal sinus
B1...00	Malignant neoplasm of digestive organs and peritoneum
B510.00	Malignant neoplasm cerebrum (excluding lobes and ventricles)
B335z00	Malignant neoplasm of skin of trunk, excluding scrotum, NOS
B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS

B552.00	Malignant neoplasm of abdomen
B506.00	Malignant neoplasm of choroid
B30z.00	Malignant neoplasm of bone and articular cartilage NOS
B160.00	Malignant neoplasm of gallbladder
B333400	Malignant neoplasm of skin of nose (external)
B572.00	Secondary malignant neoplasm of pleura
B060.00	Malignant neoplasm of tonsil
B550400	Malignant neoplasm of neck NOS
B0z0.00	Malignant neoplasm of pharynx unspecified
B18z.00	Malignant neoplasm of retroperitoneum and peritoneum NOS
BBg2.00	[M]Malignant lymphoma, non Hodgkin's type
B58z.00	Secondary malignant neoplasm of other specified site NOS
B302.00	Malignant neoplasm of vertebral column
B58y000	Secondary malignant neoplasm of breast
B151.00	Malignant neoplasm of intrahepatic bile ducts
B432.00	Malignant neoplasm of overlapping lesion of corpus uteri
BBL7112	[M]Wilms' tumour
BBF..00	[M]Soft tissue tumours and sarcomas NOS
B221000	Malignant neoplasm of carina of bronchus
1J08.00	Suspected prostate cancer
B300A00	Malignant neoplasm of maxilla
B1z0.00	Malignant neoplasm of intestinal tract, part unspecified
B481.00	Malignant neoplasm of glans penis
B62x.00	Malignant lymphoma otherwise specified
B042.00	Malignant neoplasm, overlapping lesion of floor of mouth
BBC7.00	[M]Sertoli-Leydig cell tumour
B330.00	Malignant neoplasm of skin of lip
BBf0.00	[M]Granular cell tumour NOS
B30..00	Malignant neoplasm of bone and articular cartilage
B33y.00	Malignant neoplasm of other specified skin sites
B120.00	Malignant neoplasm of duodenum
Rheumatoid	
Nyu1G00	[X]Seropositive rheumatoid arthritis, unspecified
N042z00	Rheumatoid arthropathy + visceral/systemic involvement NOS
N041.00	Felty's syndrome
G5yA.00	Rheumatoid carditis
H570.00	Rheumatoid lung
Nyu1100	[X]Other seropositive rheumatoid arthritis
N042.00	Other rheumatoid arthropathy + visceral/systemic involvement
Nyu1G00	[X]Seropositive rheumatoid arthritis, unspecified
N047.00	Seropositive errosive rheumatoid arthritis
N040R00	Rheumatoid nodule
Nyu1000	[X]Rheumatoid arthritis+involvement/other organs or systems
N04y200	Adult-onset Still's disease
Nyu1200	[X]Other specified rheumatoid arthritis
N040.00	Rheumatoid arthritis
N042100	Rheumatoid lung disease
G5y8.00	Rheumatoid myocarditis
2G25.00	O/E - hands - ulnar deviation
2G25.11	O/E - ulnar deviation
2G27.00	O/E-hands-rheumatoid spindling
66H..13	Rheumatoid arthrit. monitoring
F371200	Polyneuropathy in rheumatoid arthritis
F396400	Myopathy due to rheumatoid arthritis
G5y8.00	Rheumatoid myocarditis

G5yA.00	Rheumatoid carditis
H570.00	Rheumatoid lung
N005.00	Adult Still's Disease
N04..00	Rheumatoid arthritis and other inflammatory polyarthropathy
N040.00	Rheumatoid arthritis
N040000	Rheumatoid arthritis of cervical spine
N040100	Other rheumatoid arthritis of spine
N040200	Rheumatoid arthritis of shoulder
N040500	Rheumatoid arthritis of elbow
N040600	Rheumatoid arthritis of distal radio-ulnar joint
N040700	Rheumatoid arthritis of wrist
N040800	Rheumatoid arthritis of MCP joint
N040900	Rheumatoid arthritis of PIP joint of finger
N040A00	Rheumatoid arthritis of DIP joint of finger
N040B00	Rheumatoid arthritis of hip
N040D00	Rheumatoid arthritis of knee
N040F00	Rheumatoid arthritis of ankle
N040G00	Rheumatoid arthritis of subtalar joint
N040H00	Rheumatoid arthritis of talonavicular joint
N040J00	Rheumatoid arthritis of other tarsal joint
N040K00	Rheumatoid arthritis of 1st MTP joint
N040N00	Rheumatoid vasculitis
N040P00	Seronegative rheumatoid arthritis
N040Q00	Rheumatoid bursitis
N040R00	Rheumatoid nodule
N040S00	Rheumatoid arthritis - multiple joint
N040T00	Flare of rheumatoid arthritis
N041.00	Felty's syndrome
N042.00	Other rheumatoid arthropathy + visceral/systemic involvement
N042100	Rheumatoid lung disease
N042200	Rheumatoid nodule
N042z00	Rheumatoid arthropathy + visceral/systemic involvement NOS
N043.00	Juvenile rheumatoid arthritis - Still's disease
N043000	Juvenile rheumatoid arthropathy unspecified
N043100	Acute polyarticular juvenile rheumatoid arthritis
N043200	Pauciarticular juvenile rheumatoid arthritis
N043300	Monarticular juvenile rheumatoid arthritis
N043z00	Juvenile rheumatoid arthritis NOS
N045.00	Other juvenile arthritis
N045000	Juvenile ankylosing spondylitis
N045100	Juvenile seronegative polyarthritis
N045500	Juvenile rheumatoid arthritis
N045600	Pauciarticular onset juvenile chronic arthritis
N047.00	Seropositive errosive rheumatoid arthritis
N04X.00	Seropositive rheumatoid arthritis; unspecified
N04y000	Rheumatoid lung
N04y011	Caplan's syndrome
N04y012	Fibrosing alveolitis associated with rheumatoid arthritis
N04y200	Adult-onset Still's disease
N362200	Swan-neck finger deformity
Nyu1100	[X]Other seropositive rheumatoid arthritis
Nyu1200	[X]Other specified rheumatoid arthritis
Nyu1500	[X]Other juvenile arthritis
Nyu1G00	[X]Seropositive rheumatoid arthritis; unspecified

Table 1.4 – Comorbidities Conditions

Read Code	Term
Depression	
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt
Eu33y00	[X]Other recurrent depressive disorders
E112z00	Single major depressive episode NOS
E113.00	Recurrent major depressive episode
Eu33.00	[X]Recurrent depressive disorder
Eu41200	[X]Mixed anxiety and depressive disorder
Eu32200	[X]Severe depressive episode without psychotic symptoms
Eu25100	[X]Schizoaffective disorder, depressive type
Eu32000	[X]Mild depressive episode
Eu32100	[X]Moderate depressive episode
212S.00	Depression resolved
Eu32y00	[X]Other depressive episodes
Eu32500	[X]Major depression, mild
Eu33400	[X]Recurrent depressive disorder, currently in remission
Eu32212	[X]Single episode major depression w'out psychotic symptoms
E291.00	Prolonged depressive reaction
Eu32800	[X]Major depression, severe with psychotic symptoms
E11y200	Atypical depressive disorder
Eu34100	[X]Dysthymia
Eu32z00	[X]Depressive episode, unspecified
Eu20400	[X]Post-schizophrenic depression
E11z200	Masked depression
E135.00	Agitated depression
E130.00	Reactive depressive psychosis
Eu32z00	[X]Depressive episode, unspecified
Eu33z00	[X]Recurrent depressive disorder, unspecified
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp
E118.00	Seasonal affective disorder
Eu33000	[X]Recurrent depressive disorder, current episode mild
Eu32600	[X]Major depression, moderately severe
Eu32400	[X]Mild depression
E002100	Senile dementia with depression
Eu33100	[X]Recurrent depressive disorder, current episode moderate
E200300	Anxiety with depression
E001300	Presenile dementia with depression
Eu32300	[X]Severe depressive episode with psychotic symptoms
E2B1.00	Chronic depression
E2B..00	Depressive disorder NEC
1465	H/O: depression
1B17.00	Depressed

Read Code	Term
1B17.11	C/O - feeling depressed
1B1U.00	Symptoms of depression
1B1U.11	Depressive symptoms
1BT..00	Depressed mood
212S.00	Depression resolved
2257	O/E - depressed
62T1.00	Puerperal depression
8CAa.00	Patient given advice about management of depression
8HHq.00	Referral for guided self-help for depression
9H90.00	Depression annual review
9H91.00	Depression medication review
9H92.00	Depression interim review
9HA0.00	On depression register
9HA1.00	Removed from depression register
E001300	Presenile dementia with depression
E002100	Senile dementia with depression
E004300	Arteriosclerotic dementia with depression
E112.00	Single major depressive episode
E112000	Single major depressive episode; unspecified
E112100	Single major depressive episode; mild
E112.11	Agitated depression
E112.12	Endogenous depression first episode
E112.13	Endogenous depression first episode
E112.14	Endogenous depression
E112200	Single major depressive episode; moderate
E112300	Single major depressive episode; severe; without psychosis
E112500	Single major depressive episode; partial or unspec remission
E112600	Single major depressive episode; in full remission
E112z00	Single major depressive episode NOS
E113.00	Recurrent major depressive episode
E113000	Recurrent major depressive episodes; unspecified
E113100	Recurrent major depressive episodes; mild
E113.11	Endogenous depression - recurrent
E113200	Recurrent major depressive episodes; moderate
E113300	Recurrent major depressive episodes; severe; no psychosis
E113500	Recurrent major depressive episodes;partial/unspec remission
E113600	Recurrent major depressive episodes; in full remission
E113700	Recurrent depression
E113z00	Recurrent major depressive episode NOS
E118.00	Seasonal affective disorder
E11y200	Atypical depressive disorder
E11z200	Masked depression
E135.00	Agitated depression

Read Code	Term
E200300	Anxiety with depression
E204.00	Neurotic depression reactive type
E204.11	Postnatal depression
E211200	Depressive personality disorder
E290.00	Brief depressive reaction
E290z00	Brief depressive reaction NOS
E291.00	Prolonged depressive reaction
E2B..00	Depressive disorder NEC
E2B0.00	Postviral depression
E2B1.00	Chronic depression
Eu32.11	[X]Single episode of depressive reaction
Eu32.12	[X]Single episode of psychogenic depression
Eu32.13	[X]Single episode of reactive depression
Eu33.11	[X]Recurrent episodes of depressive reaction
Eu33.12	[X]Recurrent episodes of psychogenic depression
Eu33.13	[X]Recurrent episodes of reactive depression
Eu33.14	[X]Seasonal depressive disorder
Eu33.15	[X]SAD - Seasonal affective disorder
Eu34100	[X]Dysthymia
Eu34111	[X]Depressive neurosis
Eu34113	[X]Neurotic depression
Eu34114	[X]Persistant anxiety depression
Eu3y111	[X]Recurrent brief depressive episodes
Eu41200	[X]Mixed anxiety and depressive disorder
Eu41211	[X]Mild anxiety depression
Eu53011	[X]Postnatal depression NOS
Eu53012	[X]Postpartum depression NOS
Eu92000	[X]Depressive conduct disorder
2960AC	CHRONIC AGITATED DEPRESSION
2960AD	DEPRESSION AGITATED
2962A	DEPRESSION CHRONIC
2962AF	REACTION DEPRESSIVE AFFECTIVE
2962B	DEPRESSION ACUTE
2962EN	ENDOGENOUS DEPRESSION
2962R	RECURRENT DEPRESSION
3000E	ANXIETY DEPRESSION
3004	NEUROSIS DEPRESSIVE
3004A	DEPRESSION
3004AB	OBSERVED DEPRESSION
3004AM	MOOD DEPRESSED
3004B	PREGNANCY DEPRESSION
3004C	PUERPERAL DEPRESSION
3004CA	POSTNATAL DEPRESSION

Read Code	Term
3004E	EXOGENOUS DEPRESSION
3004ER	REACTIVE DEPRESSION
3004M	MORNING DEPRESSION
3004PP	POSTOPERATIVE DEPRESSION
3091N	INFLUENZAL DEPRESSION
3091PF	POSTINFECTIVE DEPRESSION
3091PL	DEPRESSION POSTVIRAL
3091PN	POSTINFLUENZA DEPRESSION
7902DC	POSTVIRAL DEPRESSION
Epilepsy	
F25..00	Epilepsy
F251000	Grand mal (major) epilepsy
F250011	Epileptic absences
F250000	Petit mal (minor) epilepsy
F254000	Temporal lobe epilepsy
F25z.11	Fit (in known epileptic) NOS
F253.11	Status epilepticus
SC20000	Traumatic epilepsy
F256.00	Infantile spasms
F251300	Epileptic seizures - myoclonic
F253.00	Grand mal status
F251400	Epileptic seizures - tonic
F255011	Focal epilepsy
F251600	Grand mal seizure
F25X.00	Status epilepticus, unspecified
F256000	Hypsarrhythmia
F251500	Tonic-clonic epilepsy
F255000	Jacksonian, focal or motor epilepsy
F25z.00	Epilepsy NOS
F252.00	Petit mal status
F25y200	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset
F25yz00	Other forms of epilepsy NOS
F250.00	Generalised nonconvulsive epilepsy
F254500	Complex partial epileptic seizure
F250400	Juvenile absence epilepsy
F251200	Epileptic seizures - clonic
F25y400	Benign Rolandic epilepsy
F25A.00	Juvenile myoclonic epilepsy
F258.00	Post-ictal state
F251011	Tonic-clonic epilepsy
F256100	Salaam attacks
F254100	Psychomotor epilepsy
F250200	Epileptic seizures - atonic

Read Code	Term
F25y300	Complex partial status epilepticus
F255.00	Partial epilepsy without impairment of consciousness
F251.00	Generalised convulsive epilepsy
F255y00	Partial epilepsy without impairment of consciousness OS
F255z00	Partial epilepsy without impairment of consciousness NOS
F25B.00	Alcohol-induced epilepsy
F25F.00	Photosensitive epilepsy
F25C.00	Drug-induced epilepsy
F250300	Epileptic seizures - akinetic
F254z00	Partial epilepsy with impairment of consciousness NOS
F254.00	Partial epilepsy with impairment of consciousness
F254400	Epileptic automatism
F250500	Lennox-Gastaut syndrome
F254200	Psychosensory epilepsy
F255200	Somatosensory epilepsy
F132100	Progressive myoclonic epilepsy
F251100	Neonatal myoclonic epilepsy
F259.00	Early infant epileptic encephalopathy wth suppression bursts
F25y.00	Other forms of epilepsy
F256.12	West syndrome
F255600	Simple partial epileptic seizure
F251z00	Generalised convulsive epilepsy NOS
F250z00	Generalised nonconvulsive epilepsy NOS
F251y00	Other specified generalised convulsive epilepsy
F255100	Sensory induced epilepsy
F256z00	Infantile spasms NOS
F251111	Otohara syndrome
F259.11	Ohtahara syndrome
F25y100	Gelastic epilepsy
F25y000	Cursive (running) epilepsy
F254300	Limbic system epilepsy
F255400	Visual reflex epilepsy
F25D.00	Menstrual epilepsy
F250y00	Other specified generalised nonconvulsive epilepsy
F25E.00	Stress-induced epilepsy
F255012	Motor epilepsy
F256.11	Lightning spasms
F255500	Unilateral epilepsy
F257.00	Kojevnikov's epilepsy
F255300	Visceral reflex epilepsy
F250 A	
F2510	
F25y500	Panayiotopoulos syndrome

Read Code	Term
F255311	Partial epilepsy with autonomic symptoms
F250100	Pykno-epilepsy
2126000	Epilepsy resolved
1B1W.00	Transient epileptic amnesia
2126000	Epilepsy resolved
212J.00	Epilepsy resolved
2932	PSYCHOSIS EPILEPTIC
3032EP	EPILEPSY ALCOHOLIC
3450	EPILEPSY NONCONVULSIVE GENERALIZED
3451	GRAND MAL EPILEPSY
3453AT	EPILEPSY AUTOMATISM
3453P	EPILEPSY PERIPHERAL
3453T	TEMPORAL LOBE EPILEPSY
3459A	POST-TRAUMATIC EPILEPSY
3459AB	ABDOMEN CONVULSIVE EQUIVALENT (EPILEPSY)
3459BA	IDOPATHIC EPILEPSY
3459C	EPILEPTIC COMA
3459CL	EPILEPSY CLIMACTERIC
3459D	ISCHAEMIC EPILEPSY
3459F	FIT EPILEPTIC
3459M	MIGRAINE EPILEPSY
3459N	NOCTURNAL EPILEPSY
3459R	EPILEPSY RESOLVED
667..00	Epilepsy monitoring
6672	Follow-up epilepsy assessment
6674	Epilepsy associated problems
6675	Fit frequency
6676	Last fit
6678	Epilepsy treatment changed
6679	Epilepsy treatment started
667A.00	Epilepsy treatment stopped
667B.00	Nocturnal epilepsy
667C.00	Epilepsy control good
667D.00	Epilepsy control poor
667E.00	Epilepsy care arrangement
667F.00	Seizure free >12 months
667G.00	Epilepsy restricts employment
667H.00	Epilepsy prevents employment
667J.00	Epilepsy impairs education
667K.00	Epilepsy limits activities
667L.00	Epilepsy does not limit activities
667M.00	Epilepsy management plan given
667N.00	Epilepsy severity

Read Code	Term
667P.00	No seizures on treatment
667Q.00	1 to 12 seizures a year
667R.00	2 to 4 seizures a month
667S.00	1 to 7 seizures a week
667T.00	Daily seizures
667V.00	Many seizures a day
667W.00	Emergency epilepsy treatment since last appointment
667X.00	No epilepsy drug side effects
8BIF.00	Epilepsy medication review
8BL3.00	Patient on maximal tolerated anticonvulsant therapy
9N0r.00	Seen in epilepsy clinic
9N4V.00	DNA - Did not attend epilepsy clinic
Eu05212	[X]Schizophrenia-like psychosis in epilepsy
Eu05y11	[X]Epileptic psychosis NOS
Eu06013	[X]Limbic epilepsy personality
Eu80300	[X]Acquired aphasia with epilepsy [Landau - Kleffner]
F132100	Progressive myoclonic epilepsy
F25z.00	Epilepsy NOS
F25z.11	Fit (in known epileptic) NOS
SC20000	Traumatic epilepsy
342 E	PARKINSONIAN EPILEPSY
Stroke	
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral

Read Code	Term
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G656.00	Vertebrobasilar insufficiency
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome

Read Code	Term
G667.00	Left sided CVA
G668.00	Right sided CVA
G669.00	Cerebral palsy, not congenital or infantile, acute
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
ZV12D00	[V]Personal history of transient ischaemic attack
L440.11	CVA - cerebrovascular accident in the puerperium
L440.12	Stroke in the puerperium
4350AT	TRANSIENT ISCHAEMIC ATTACKS WITH HYPERTE
4359AT	TRANSIENT ISCHAEMIC ATTACKS
4360A	CEREBROVASCULAR ACCIDENT WITH HYPERTENSI
4360B	STROKE WITH HYPERTENSION
4369A	CVA (CEREBROVASCULAR ACCIDENT)
4369AL	CEREBROVASCULAR ACCIDENT LEFT
4369AR	CEREBROVASCULAR ACCIDENT RIGHT
4369B	STROKE
4369BN	SYNDROME STROKE
COPD	
H320311	Tension pneumatocoele
H31z.00	Chronic bronchitis NOS
H312011	Chronic wheezy bronchitis
H310.00	Simple chronic bronchitis
H312200	Acute exacerbation of chronic obstructive airways disease
H32y000	Acute vesicular emphysema
H31y000	Chronic tracheitis
H321.00	Panlobular emphysema
H320100	Zonal bullous emphysema
H32y111	Acute interstitial emphysema
H312300	Bronchiolitis obliterans
H31y.00	Other chronic bronchitis
H3A..00	End stage chronic obstructive airways disease
H36..00	Mild chronic obstructive pulmonary disease
H312100	Emphysematous bronchitis
H312.00	Obstructive chronic bronchitis
H31..00	Chronic bronchitis
H310100	Smokers' cough

Read Code	Term
H31y100	Chronic tracheobronchitis
H311100	Fetid chronic bronchitis
H320000	Segmental bullous emphysema
H313.00	Mixed simple and mucopurulent chronic bronchitis
H312000	Chronic asthmatic bronchitis
H32yz00	Other emphysema NOS
H32y200	MacLeod's unilateral emphysema
H320.00	Chronic bullous emphysema
H38..00	Severe chronic obstructive pulmonary disease
H37..00	Moderate chronic obstructive pulmonary disease
H3...00	Chronic obstructive pulmonary disease
H310z00	Simple chronic bronchitis NOS
H39..00	Very severe chronic obstructive pulmonary disease
H310000	Chronic catarrhal bronchitis
H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn
H320300	Bullous emphysema with collapse
H32..00	Emphysema
H3y..00	Other specified chronic obstructive airways disease
H320z00	Chronic bullous emphysema NOS
H3y..11	Other specified chronic obstructive pulmonary disease
H312z00	Obstructive chronic bronchitis NOS
H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec
H32z.00	Emphysema NOS
H31yz00	Other chronic bronchitis NOS
H3z..00	Chronic obstructive airways disease NOS
H32y100	Atrophic (senile) emphysema
H32y.00	Other emphysema
H311000	Purulent chronic bronchitis
H311z00	Mucopurulent chronic bronchitis NOS
H311.00	Mucopurulent chronic bronchitis
H320200	Giant bullous emphysema
H322.00	Centrilobular emphysema
491 E	CHRONIC BRONCHITIS WITH EMPHYSEMA
492 AC	EMPHYSEMA APICAL BULLAE
5199G	OBSTRUCTIVE AIRWAYS DISEASE CHRONIC
5199GL	COLD (CHRONIC OBSTRUCTIVE LUNG DISEASE)
5199GP	COPD (CHRONIC OBSTRUCTIVE PULMONARY DISE
Diabetes 1&2	
C10..00	Diabetes mellitus
C109J00	Insulin treated Type 2 diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10C.00	Diabetes mellitus autosomal dominant
C10D.00	Diabetes mellitus autosomal dominant type 2

Read Code	Term
C10E.00	Type 1 diabetes mellitus
C10E.11	Type I diabetes mellitus
C10E.12	Insulin dependent diabetes mellitus
C10E000	Type 1 diabetes mellitus with renal complications
C10E012	Insulin-dependent diabetes mellitus with renal complications
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E200	Type 1 diabetes mellitus with neurological complications
C10E212	Insulin-dependent diabetes mellitus with neurological comps
C10E300	Type 1 diabetes mellitus with multiple complications
C10E311	Type I diabetes mellitus with multiple complications
C10E312	Insulin dependent diabetes mellitus with multiple complicat
C10E400	Unstable type 1 diabetes mellitus
C10E411	Unstable type I diabetes mellitus
C10E412	Unstable insulin dependent diabetes mellitus
C10E500	Type 1 diabetes mellitus with ulcer
C10E511	Type I diabetes mellitus with ulcer
C10E512	Insulin dependent diabetes mellitus with ulcer
C10E600	Type 1 diabetes mellitus with gangrene
C10E611	Type I diabetes mellitus with gangrene
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10E800	Type 1 diabetes mellitus - poor control
C10E812	Insulin dependent diabetes mellitus - poor control
C10E900	Type 1 diabetes mellitus maturity onset
C10E911	Type I diabetes mellitus maturity onset
C10E912	Insulin dependent diabetes maturity onset
C10EA00	Type 1 diabetes mellitus without complication
C10EA11	Type I diabetes mellitus without complication
C10EA12	Insulin-dependent diabetes without complication
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10EC00	Type 1 diabetes mellitus with polyneuropathy
C10EC11	Type I diabetes mellitus with polyneuropathy
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
C10ED00	Type 1 diabetes mellitus with nephropathy
C10ED12	Insulin dependent diabetes mellitus with nephropathy
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10EF00	Type 1 diabetes mellitus with diabetic cataract
C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
C10EG00	Type 1 diabetes mellitus with peripheral angiopathy

Read Code	Term
C10EH00	Type 1 diabetes mellitus with arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C10EK00	Type 1 diabetes mellitus with persistent proteinuria
C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
C10EL11	Type I diabetes mellitus with persistent microalbuminuria
C10EM00	Type 1 diabetes mellitus with ketoacidosis
C10EM11	Type I diabetes mellitus with ketoacidosis
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C10EN11	Type I diabetes mellitus with ketoacidotic coma
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10EQ00	Type 1 diabetes mellitus with gastroparesis
C10ER00	Latent autoimmune diabetes mellitus in adult
C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C10F111	Type II diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications
C10F211	Type II diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F511	Type II diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F800	Reaven's syndrome
C10F811	Metabolic syndrome X
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma

Read Code	Term
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FG11	Type II diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Type II diabetes mellitus with persistent proteinuria
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10FR00	Type 2 diabetes mellitus with gastroparesis
C10FS00	Maternally inherited diabetes mellitus
C10G.00	Secondary pancreatic diabetes mellitus
C10G000	Secondary pancreatic diabetes mellitus without complication
C10H.00	Diabetes mellitus induced by non-steroid drugs
C10H000	DM induced by non-steroid drugs without complication
C10M.00	Lipoatrophic diabetes mellitus
C10N.00	Secondary diabetes mellitus
C10N000	Secondary diabetes mellitus without complication
C10N100	Cystic fibrosis related diabetes mellitus
66Ao.00	Diabetes type 2 review
66At100	Type II diabetic dietary review
66At111	Type 2 diabetic dietary review
C100112	Non-insulin dependent diabetes mellitus
C109.00	Non-insulin dependent diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C109011	Type II diabetes mellitus with renal complications
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109.12	Type 2 diabetes mellitus
C109.13	Type II diabetes mellitus
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Type II diabetes mellitus with neurological complications
C109212	Type 2 diabetes mellitus with neurological complications

Read Code	Term
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109511	Type II diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109711	Type II diabetes mellitus - poor control
C109712	Type 2 diabetes mellitus - poor control
C109900	Non-insulin-dependent diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C109E11	Type II diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract
C109F11	Type II diabetes mellitus with peripheral angiopathy
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10D.00	Diabetes mellitus autosomal dominant type 2
C10F.00	Type 2 diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications

Read Code	Term
C10F.11	Type II diabetes mellitus
C10F111	Type II diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications
C10F211	Type II diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F511	Type II diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FG11	Type II diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Type II diabetes mellitus with persistent proteinuria
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10FR00	Type 2 diabetes mellitus with gastroparesis
ZC2CA00	Dietary advice for type II diabetes
C10FF11	Type II diabetes mellitus with peripheral angiopathy

Read Code	Term
C10FP11	Type II diabetes mellitus with ketoacidotic coma
C10FN11	Type II diabetes mellitus with ketoacidosis
C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
C10FB11	Type II diabetes mellitus with polyneuropathy
Heartfail	
G584.00	Right ventricular failure
G58z.11	Weak heart
G58..11	Cardiac failure
G582.00	Acute heart failure
G58..00	Heart failure
662g.00	New York Heart Association classification - class II
662f.00	New York Heart Association classification - class I
G583.00	Heart failure with normal ejection fraction
G580.14	Biventricular failure
G581.13	Impaired left ventricular function
G58z.12	Cardiac failure NOS
662F.00	Hypertension treatm. started
662G.00	Hypertensive treatm.changed
G581.12	Pulmonary oedema - acute
G580000	Acute congestive heart failure
G581.00	Left ventricular failure
G580200	Decompensated cardiac failure
G581000	Acute left ventricular failure
G580300	Compensated cardiac failure
G58z.00	Heart failure NOS
G580.00	Congestive heart failure
G580.13	Right ventricular failure
G581.11	Asthma - cardiac
G580.12	Right heart failure
G580400	Congestive heart failure due to valvular disease
662H.00	Hypertension treatm.stopped
G580.11	Congestive cardiac failure
G1yz100	Rheumatic left ventricular failure
662i.00	New York Heart Association classification - class IV
662h.00	New York Heart Association classification - class III
G580100	Chronic congestive heart failure
G583.11	HFNEF - heart failure with normal ejection fraction
1O1..00	Heart failure confirmed
G1yz100	Rheumatic left ventricular failure
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
Q48y100	Congenital cardiac failure
Q490.00	Neonatal cardiac failure

Read Code	Term
14A6.00	H/O: heart failure
14AM.00	H/O: Heart failure in last year
1O1..00	Heart failure confirmed
585f.00	Echocardiogram shows left ventricular systolic dysfunction
585g.00	Echocardiogram shows left ventricular diastolic dysfunction
662f.00	New York Heart Association classification - class I
662g.00	New York Heart Association classification - class II
662h.00	New York Heart Association classification - class III
662i.00	New York Heart Association classification - class IV
662p.00	Heart failure 6 month review
662T.00	Congestive heart failure monitoring
662W.00	Heart failure annual review
8B29.00	Cardiac failure therapy
8CL3.00	Heart failure care plan discussed with patient
8H2S.00	Admit heart failure emergency
8HBE.00	Heart failure follow-up
8HHb.00	Referral to heart failure nurse
8HHz.00	Referral to heart failure exercise programme
8Hk0.00	Referred to heart failure education group
8HTL.00	Referral to heart failure clinic
9N0k.00	Seen in heart failure clinic
9N2p.00	Seen by community heart failure nurse
9N6T.00	Referred by heart failure nurse specialist
G1yz100	Rheumatic left ventricular failure
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
G58..00	Heart failure
G580.00	Congestive heart failure
G580000	Acute congestive heart failure
G580100	Chronic congestive heart failure
G580.11	Congestive cardiac failure
G580.12	Right heart failure
G580.13	Right ventricular failure
G580.14	Biventricular failure
G580200	Decompensated cardiac failure
G580300	Compensated cardiac failure
G581.00	Left ventricular failure
G581000	Acute left ventricular failure
G58..11	Cardiac failure
G581.11	Asthma - cardiac
G581.12	Pulmonary oedema - acute
G581.13	Impaired left ventricular function
G582.00	Acute heart failure

Read Code	Term
G58z.00	Heart failure NOS
G58z.11	Weak heart
G58z.12	Cardiac failure NOS
G5y4z00	Post cardiac operation heart failure NOS
G5yy900	Left ventricular systolic dysfunction
G5yyA00	Left ventricular diastolic dysfunction
Q48y100	Congenital cardiac failure
Q490.00	Neonatal cardiac failure
SP11100	Cardiac insufficiency as a complication of care
SP11111	Heart failure as a complication of care
402 C	HYPERTENSION CONGESTIVE HEART FAILURE
4270C	CONGESTIVE CARDIAC FAILURE
4270CC	CONGESTIVE HEART FAILURE COMPENSATED
4270D	CONGESTIVE HEART FAILURE DECOMPENSATED
4270DR	DROPSY CARDIAC
4270LW	SYNDROME LOW-OUTPUT
4270R	HEART FAILURE RIGHT-SIDED
4271	LVF (LEFT VENTRICULAR FAILURE)
4271A	LEFT VENTRICULAR FAILURE ACUTE
4271H	HEART FAILURE LEFT-SIDED
428 A	INSUFFICIENCY CARDIAC
7824A	HIGH OUTPUT FAILURE (CARDIAC)
7824AC	HEART FAILURE ACUTE
7824FC	FAILURE CARDIAC
7824FH	HEART FAILURE
Atrial Fibrillation	
G573z00	Atrial fibrillation and flutter NOS
G573000	Atrial fibrillation
G573300	Non-rheumatic atrial fibrillation
G573500	Persistent atrial fibrillation
G573200	Paroxysmal atrial fibrillation
G573100	Atrial flutter
G573.00	Atrial fibrillation and flutter
G573400	Permanent atrial fibrillation
3272	ECG: atrial fibrillation
14AN.00	H/O: atrial fibrillation
662S.00	Atrial fibrillation monitoring
6A9..00	Atrial fibrillation annual review
8HTy.00	Referral to atrial fibrillation clinic
CHD Codes	
G3...00	Ischaemic heart disease
G30..00	Acute myocardial infarction
G30..14	Heart attack

Read Code	Term
G340.12	Coronary artery disease
G33z300	Angina on effort
G33..00	Angina pectoris
G311.13	Unstable angina
G340.11	Triple vessel disease of the heart
G3z..00	Ischaemic heart disease NOS
G30..15	MI - acute myocardial infarction
G308.00	Inferior myocardial infarction NOS
G3...13	IHD - Ischaemic heart disease
G30..12	Coronary thrombosis
G307.00	Acute subendocardial infarction
G340000	Single coronary vessel disease
G32..00	Old myocardial infarction
G311.11	Crescendo angina
G340100	Double coronary vessel disease
G301.00	Other specified anterior myocardial infarction
G340.00	Coronary atherosclerosis
G343.00	Ischaemic cardiomyopathy
G311100	Unstable angina
G33z200	Syncope anginosa
G302.00	Acute inferolateral infarction
G31y000	Acute coronary insufficiency
G31y.00	Other acute and subacute ischaemic heart disease
G307000	Acute non-Q wave infarction
G33z500	Post infarct angina
G307100	Acute non-ST segment elevation myocardial infarction
G311500	Acute coronary syndrome
G300.00	Acute anterolateral infarction
G30X000	Acute ST segment elevation myocardial infarction
G33z700	Stable angina
G30..11	Attack - heart
G30..16	Thrombosis - coronary
G30z.00	Acute myocardial infarction NOS
G301z00	Anterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G310.11	Dressler's syndrome
G34z.00	Other chronic ischaemic heart disease NOS
G32..11	Healed myocardial infarction
G311200	Angina at rest
G32..12	Personal history of myocardial infarction
G30..17	Silent myocardial infarction
G301100	Acute anteroseptal infarction
G311400	Worsening angina

Read Code	Term
G330000	Nocturnal angina
G35..00	Subsequent myocardial infarction
G34z000	Asymptomatic coronary heart disease
G311.14	Angina at rest
G330.00	Angina decubitus
G3...12	Atherosclerotic heart disease
G31y300	Transient myocardial ischaemia
G3y..00	Other specified ischaemic heart disease
G34y100	Chronic myocardial ischaemia
G310.00	Postmyocardial infarction syndrome
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G304.00	Posterior myocardial infarction NOS
G360.00	Haemopericardium/current comp folow acut myocard infarct
G34y000	Chronic coronary insufficiency
G3...11	Arteriosclerotic heart disease
G33z.00	Angina pectoris NOS
G33z600	New onset angina
G31..00	Other acute and subacute ischaemic heart disease
G31yz00	Other acute and subacute ischaemic heart disease NOS
G34..00	Other chronic ischaemic heart disease
G33zz00	Angina pectoris NOS
G30y000	Acute atrial infarction
G344.00	Silent myocardial ischaemia
G303.00	Acute inferoposterior infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G330z00	Angina decubitus NOS
G309.00	Acute Q-wave infarct
G30..13	Cardiac rupture following myocardial infarction (MI)
G38..00	Postoperative myocardial infarction
G33z400	Ischaemic chest pain
G30B.00	Acute posterolateral myocardial infarction
G311300	Refractory angina
G34y.00	Other specified chronic ischaemic heart disease
G30y.00	Other acute myocardial infarction
G34yz00	Other specified chronic ischaemic heart disease NOS
G36..00	Certain current complication follow acute myocardial infarct
G311.00	Preinfarction syndrome
G342.00	Atherosclerotic cardiovascular disease
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G351.00	Subsequent myocardial infarction of inferior wall
G312.00	Coronary thrombosis not resulting in myocardial infarction
Gyu3000	[X]Other forms of angina pectoris
G311.12	Impending infarction

Read Code	Term
G31y200	Subendocardial ischaemia
G301000	Acute anteroapical infarction
G30y200	Acute septal infarction
G384.00	Postoperative subendocardial myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G30yz00	Other acute myocardial infarction NOS
G380.00	Postoperative transmural myocardial infarction anterior wall
G35X.00	Subsequent myocardial infarction of unspecified site
G381.00	Postoperative transmural myocardial infarction inferior wall
Gyu3300	[X]Other forms of chronic ischaemic heart disease
Gyu3.00	[X]Ischaemic heart diseases
G311z00	Preinfarction syndrome NOS
G33z100	Stenocardia
G311011	MI - myocardial infarction aborted
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G311000	Myocardial infarction aborted
G30y100	Acute papillary muscle infarction
G306.00	True posterior myocardial infarction
G33z000	Status anginosus
G31y100	Microinfarction of heart
Gyu3200	[X]Other forms of acute ischaemic heart disease
G38z.00	Postoperative myocardial infarction, unspecified
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G353.00	Subsequent myocardial infarction of other sites
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3600	[X]Subsequent myocardial infarction of unspecified site
14AJ.00	H/O: Angina in last year
662K.00	Angina control
662K000	Angina control - good
662K100	Angina control - poor
662K200	Angina control - improving
662K300	Angina control - worsening
662Kz00	Angina control NOS
662N.00	CHD monitoring
6A2..00	Coronary heart disease annual review
6A4..00	Coronary heart disease review
8B27.00	Antianginal therapy
8B3k.00	Coronary heart disease medication review
8B63.11	Aspirin prophylaxis - IHD
8CR6.00	Coronary heart disease risk clinical management plan
9Ob0.00	Attends coronary heart disease monitoring
9Ob8.00	Coronary heart disease monitoring check done

Read Code	Term
4119B	ISCHAEMIC HEART DISEASE SUBACUTE
4120A	ISCHAEMIC HEART DISEASE HYPERTENSIVE
4129	ISCHAEMIC HEART DISEASE CHRONIC
4129AN	ISCHAEMIC HEART DISEASE
4129N	ISCHAEMIC HEART DISEASE ASYMPTOMATIC
4130E	ANGINA EFFORT WITH HYPERTENSION
4139	ANGINA PECTORIS
4139AA	ANGINA ATTACK
4139AT	ANGINA ATYPICAL
4139C	CARDIAC ANGINA
4139CO	ANGINA CRESCENDO
4139E	ANGINA EFFORT
4139M	SYNDROME ANGINAL
4139N	ANGINA
4139PA	ANGINA INVERSA
4139U	UNSTABLE ANGINA
4149	ASYMPTOMATIC ISCHAEMIC HEART DISEASE
Hypertension Codes	
Gyu2000	[X]Other secondary hypertension
G240.00	Secondary malignant hypertension
G20z.00	Essential hypertension NOS
G2...00	Hypertensive disease
G24z100	Hypertension secondary to drug
G203.00	Diastolic hypertension
G202.00	Systolic hypertension
G241000	Secondary benign renovascular hypertension
G20z.11	Hypertension NOS
G241.00	Secondary benign hypertension
G2y..00	Other specified hypertensive disease
G240000	Secondary malignant renovascular hypertension
G24zz00	Secondary hypertension NOS
G24z.00	Secondary hypertension NOS
G244.00	Hypertension secondary to endocrine disorders
G24..00	Secondary hypertension
G200.00	Malignant essential hypertension
G20..11	High blood pressure
Gyu2.00	[X]Hypertensive diseases
G201.00	Benign essential hypertension
G24z000	Secondary renovascular hypertension NOS
G2z..00	Hypertensive disease NOS
G240z00	Secondary malignant hypertension NOS
G20..00	Essential hypertension
G241z00	Secondary benign hypertension NOS

Appendix 2 Drug Product Codes

Prodcode	Drug Substance	Prodcode	Drug Substance
22	Fluoxetine hydrochloride	40165	Paroxetine hydrochloride
49	Amitriptyline hydrochloride	40277	Venlafaxine hydrochloride
50	Paroxetine hydrochloride	40295	Agomelatine
67	Citalopram hydrobromide	40396	Amitriptyline hydrochloride
74	Dosulepin hydrochloride	40407	Venlafaxine Hydrochloride
83	Amitriptyline hydrochloride	40494	Agomelatine
84	Dosulepin hydrochloride	40514	Venlafaxine hydrochloride
114	Lofepramine hydrochloride	40515	Venlafaxine hydrochloride
252	Fluoxetine hydrochloride	40517	Venlafaxine hydrochloride
301	Venlafaxine hydrochloride	40726	Escitalopram Oxalate
418	Fluoxetine hydrochloride	40764	Venlafaxine hydrochloride
470	Venlafaxine hydrochloride	40777	Doxepin Hydrochloride
476	Citalopram hydrobromide	40815	Venlafaxine hydrochloride
488	Sertraline hydrochloride	40817	Venlafaxine hydrochloride
513	Citalopram hydrochloride	40892	Paroxetine hydrochloride
527	Paroxetine hydrochloride	40917	Venlafaxine hydrochloride
595	Amitriptyline hydrochloride/Perphenazine	41033	Venlafaxine hydrochloride
600	Flupentixol dihydrochloride	41062	Escitalopram Oxalate
603	Escitalopram oxalate	41299	Venlafaxine hydrochloride
623	Venlafaxine hydrochloride	41314	Venlafaxine hydrochloride
648	Escitalopram oxalate	41408	Imipramine hydrochloride
727	Sertraline hydrochloride	41528	Citalopram hydrobromide
742	Mirtazapine	41563	Clomipramine hydrochloride
785	Escitalopram oxalate	41597	Clomipramine hydrochloride
815	Citalopram hydrochloride	41609	Trazodone hydrochloride
841	Paroxetine hydrochloride	41627	Lofepramine hydrochloride
1169	Dosulepin hydrochloride	41628	Clomipramine hydrochloride
1208	Amitriptyline hydrochloride/Perphenazine	41654	Tranylcypromine sulfate
1222	Venlafaxine hydrochloride	41681	Imipramine hydrochloride
1310	Imipramine hydrochloride	41709	Trazodone hydrochloride
1397	Paroxetine hydrochloride	41710	Trazodone hydrochloride
1453	Amitriptyline hydrochloride/Perphenazine	41729	Amitriptyline hydrochloride
1474	Venlafaxine hydrochloride	41731	Isocarboxazid
1575	Paroxetine hydrochloride	42078	Amitriptyline hydrochloride
1612	Sertraline hydrochloride	42107	Fluoxetine hydrochloride
Prodcode	**Drug Substance**	**Prodcode**	**Drug Substance**

1712	Citalopram hydrobromide	42228	Trimipramine maleate
1730	Trazodone hydrochloride	42247	Imipramine hydrochloride
1809	Imipramine hydrochloride	42387	Sertraline hydrochloride
1888	Amitriptyline hydrochloride	42394	Amitriptyline hydrochloride
1940	Dosulepin hydrochloride	42499	Fluoxetine hydrochloride
2039	Trimipramine maleate	42600	Venlafaxine hydrochloride
2093	Lofepramine hydrochloride	42660	Citalopram hydrobromide
2275	Flupentixol dihydrochloride	42734	Dosulepin hydrochloride
2290	Fluvoxamine maleate	42803	Fluoxetine hydrochloride
2320	Dosulepin hydrochloride	43024	Dosulepin hydrochloride
2356	Reboxetine mesilate	43203	Venlafaxine hydrochloride
2408	Citalopram hydrobromide	43234	Mirtazapine
2525	Amitriptyline Hydrochloride	43235	Mirtazapine
2531	Trimipramine maleate	43236	Mirtazapine
2532	Trimipramine maleate	43237	Mirtazapine
2548	Fluoxetine hydrochloride	43239	Mirtazapine
2579	Imipramine hydrochloride	43241	Mirtazapine
2654	Venlafaxine hydrochloride	43242	Mirtazapine
2880	Fluvoxamine maleate	43246	Mirtazapine
2897	Fluvoxamine maleate	43247	Mirtazapine
3083	Mianserin hydrochloride	43248	Mirtazapine
3183	Nortriptyline hydrochloride	43250	Mirtazapine
3194	Clomipramine hydrochloride	43253	Mirtazapine
3196	Trimipramine maleate	43256	Mirtazapine
3349	Phenelzine sulfate	43257	Mirtazapine
3355	Trazodone hydrochloride	43334	Venlafaxine hydrochloride
3391	Nefazodone hydrochloride	43518	Fluvoxamine maleate
3554	Doxepin hydrochloride	43519	Citalopram hydrobromide
3601	Paroxetine hydrochloride	43534	Lofepramine hydrochloride
3652	Amoxapine	43561	Clomipramine hydrochloride
3657	Clomipramine hydrochloride	43673	Venlafaxine hydrochloride
3670	Clomipramine hydrochloride	43968	Venlafaxine hydrochloride
3777	Amitriptyline Hydrochloride	44853	Dosulepin hydrochloride
3783	Tranylcypromine sulfate	44861	Fluvoxamine maleate
3842	Doxepin hydrochloride	44936	Venlafaxine hydrochloride
3861	Citalopram hydrobromide	44937	Venlafaxine hydrochloride
3903	Nortriptyline hydrochloride	44944	Sertraline hydrochloride
3925	Clomipramine hydrochloride	45223	Citalopram hydrobromide
3951	Flupentixol dihydrochloride	45224	Fluoxetine hydrochloride
3953	Flupentixol dihydrochloride	45226	Trimipramine maleate
4003	Trazodone hydrochloride	45233	Amitriptyline hydrochloride
Prodcode	**Drug Substance**	**Prodcode**	**Drug Substance**

4011	Nefazodone hydrochloride	45242	Amitriptyline hydrochloride
4020	Trazodone hydrochloride	45247	Fluoxetine hydrochloride
4075	Fluoxetine hydrochloride	45286	Citalopram hydrobromide
4118	Nortriptyline Hydrochloride	45304	Citalopram hydrobromide
4194	Trazodone hydrochloride	45316	Fluoxetine hydrochloride
4218	Lofepramine hydrochloride	45318	Clomipramine hydrochloride
4297	Nefazodone hydrochloride	45329	Fluoxetine hydrochloride
4310	Trimipramine maleate	45350	Clomipramine hydrochloride
4321	Phenelzine sulfate	45664	Venlafaxine hydrochloride
4352	Sertraline hydrochloride	45737	Dosulepin Hydrochloride
4411	Amoxapine	45806	Venlafaxine Hydrochloride
4422	Tryptophan	45818	Venlafaxine Hydrochloride
4554	Nefazodone hydrochloride	45915	Sertraline hydrochloride
4690	Amitriptyline hydrochloride	45959	Venlafaxine hydrochloride
4726	Mirtazapine	46668	Mirtazapine
4770	Citalopram hydrobromide	46801	Amitriptyline hydrochloride
4874	Trazodone hydrochloride	46818	Amitriptyline hydrochloride
4907	Fluoxetine hydrochloride	46926	Citalopram hydrobromide
5073	Doxepin hydrochloride	46970	Amitriptyline hydrochloride
5611	Tryptophan	46977	Citalopram hydrobromide
5710	Venlafaxine hydrochloride	47363	Mianserin hydrochloride
6054	Dosulepin Hydrochloride	47945	Mirtazapine
6218	Escitalopram oxalate	47966	Mirtazapine
6255	Mianserin hydrochloride	48026	Citalopram hydrobromide
6312	Amitriptyline hydrochloride	48045	Fluvoxamine maleate
6360	Escitalopram oxalate	48065	Amitriptyline Hydrochloride
6405	Escitalopram oxalate	48199	Venlafaxine hydrochloride
6421	Mirtazapine	48216	Nortriptyline hydrochloride
6442	Trazodone hydrochloride	48220	Fluoxetine hydrochloride
6481	Mirtazapine	48698	Mirtazapine
6488	Mirtazapine	49165	Citalopram hydrobromide
6795	Mirtazapine	49511	Venlafaxine hydrochloride
6846	Mirtazapine	49519	Sertraline hydrochloride
6854	Mirtazapine	49820	Mirtazapine
6894	Amitriptyline Hydrochloride/Perphenazine	50081	Venlafaxine hydrochloride
7059	Doxepin hydrochloride	50592	Flupentixol dihydrochloride
7328	Sertraline hydrochloride	50722	Dosulepin hydrochloride
7468	Mianserin hydrochloride	50892	Mirtazapine
7515	Clomipramine hydrochloride	50934	Venlafaxine hydrochloride
Prodcode	**Drug Substance**	**Prodcode**	**Drug Substance**

7677	Nortriptyline hydrochloride	51280	Venlafaxine hydrochloride
7678	Nortriptyline Hydrochloride	51361	Venlafaxine hydrochloride
7693	Clomipramine hydrochloride	51699	Venlafaxine hydrochloride
7751	Amitriptyline hydrochloride	51758	Dosulepin hydrochloride
7755	Protriptyline Hydrochloride	52074	Venlafaxine hydrochloride
7756	Protriptyline Hydrochloride	52100	Citalopram hydrobromide
7816	Protriptyline Hydrochloride	52354	Citalopram hydrobromide
7894	Clomipramine hydrochloride	52408	Citalopram hydrobromide
7910	Imipramine hydrochloride	52516	Venlafaxine hydrochloride
7979	Desipramine	52607	Citalopram hydrobromide
7981	Desipramine	52716	Venlafaxine hydrochloride
8144	Mianserin hydrochloride	52824	Citalopram hydrobromide
8174	Trazodone hydrochloride	52867	Amitriptyline hydrochloride
8332	Amitriptyline hydrochloride	53161	Clomipramine hydrochloride
8585	Mianserin hydrochloride	53187	Clomipramine hydrochloride
8640	Nortriptyline hydrochloride	53321	Mirtazapine
8661	Clomipramine hydrochloride	53326	Venlafaxine hydrochloride
8719	Clomipramine hydrochloride	53394	Citalopram hydrobromide
8720	Clomipramine hydrochloride	53543	Mirtazapine
8726	Amitriptyline hydrochloride	53648	Mirtazapine
8831	Amitriptyline Hydrochloride	53699	Mirtazapine
8878	Amitriptyline Hydrochloride	53787	Citalopram hydrobromide
8928	Trimipramine maleate	53808	Trimipramine maleate
9182	Venlafaxine hydrochloride	54012	Mirtazapine
9534	Nefazodone Hydrochloride	54081	Sertraline
10083	Mirtazapine	54342	Mirtazapine
10413	Doxepin hydrochloride	54644	Mirtazapine
10787	Tranylcypromine sulfate	54686	Tryptophan 500mg capsules
10948	Dosulepin Hydrochloride	54747	Sertraline
11187	Protriptyline Hydrochloride	54792	Mirtazapine
11956	Mianserin hydrochloride	54826	Sertraline hydrochloride
11963	Amitriptyline Hydrochloride/Chlordiazepoxide	54827	Citalopram hydrobromide
12111	Viloxazine Hydrochloride	54877	Amitriptyline hydrochloride
12123	Fluvoxamine maleate	54933	Sertraline hydrochloride
12125	Doxepin hydrochloride	55023	Paroxetine hydrochloride
12129	Doxepin hydrochloride	55033	Citalopram hydrobromide
12192	Mianserin hydrochloride	55137	Trazodone hydrochloride
12207	Isocarboxazid	55138	Trazodone
12221	Tryptophan	55139	Amitriptyline hydrochloride
Prodcode	**Drug Substance**	**Prodcode**	**Drug Substance**

12227	Butriptyline Hydrochloride	55146	Sertraline hydrochloride
12309	Viloxazine Hydrochloride	55424	Venlafaxine Hydrochloride
12353	Nortriptyline Hydrochloride	55482	Mirtazapine
12368	Mianserin hydrochloride	55488	Sertraline hydrochloride
12503	Isocarboxazid	55491	Amitriptyline hydrochloride
12549	Nortriptyline Hydrochloride	55501	Venlafaxine hydrochloride
13237	Venlafaxine hydrochloride	55537	Paroxetine hydrochloride
14398	Amoxapine	55970	Nortriptyline hydrochloride
14519	Doxepin hydrochloride	56009	Citalopram hydrobromide
14534	Amitriptyline Hydrochloride/Chlordiazepoxide	56209	Mirtazapine
14740	Fluoxetine hydrochloride	56229	Lofepramine hydrochloride
15163	Reboxetine mesilate	56292	Citalopram hydrochloride
15268	Mirtazapine	56355	Citalopram hydrobromide
15380	Amoxapine	56457	Venlafaxine hydrochloride
15632	Dosulepin hydrochloride	56501	Imipramine hydrochloride
16154	Mirtazapine	56662	Venlafaxine hydrochloride
16323	Amitriptyline Hydrochloride/Perphenazine	56703	Lofepramine hydrochloride
17183	Nortriptyline Hydrochloride	57107	Amitriptyline hydrochloride
17319	Amoxapine	57226	Trazodone hydrochloride
18290	Iproniazide	57532	Fluoxetine hydrochloride
18342	Amitriptyline Hydrochloride/Chlordiazepoxide	57751	Venlafaxine hydrochloride
18932	Butriptyline Hydrochloride	57926	Dosulepin hydrochloride
19168	Dosulepin Hydrochloride	57936	Citalopram hydrochloride
19181	Trazodone hydrochloride	57972	Amitriptyline hydrochloride
19183	Fluoxetine hydrochloride	57978	Trimipramine maleate
19186	Dosulepin hydrochloride	58291	Mirtazapine
19470	Fluoxetine hydrochloride	58450	Lofepramine hydrochloride
20026	Amitriptyline hydrochloride	58476	Citalopram hydrobromide
20152	Escitalopram oxalate	58625	Mirtazapine
20504	Tryptophan	58664	Sertraline hydrochloride
20571	Nortriptyline Hydrochloride/Fluphenazine Hydrochloride	58681	Venlafaxine hydrochloride
21081	Amitriptyline Hydrochloride/Chlordiazepoxide	58723	Sertraline hydrochloride
21157	Dosulepin hydrochloride	58726	Venlafaxine hydrochloride
21357	Amoxapine	58837	Venlafaxine hydrochloride
Prodcode	**Drug Substance**	**Prodcode**	**Drug Substance**

21819	Dosulepin hydrochloride	59035	Venlafaxine hydrochloride
21820	Dosulepin hydrochloride	59161	Amitriptyline hydrochloride
22070	Amitriptyline Hydrochloride	59193	Citalopram hydrobromide
23426	Dosulepin hydrochloride	59288	Paroxetine hydrochloride
24134	Amitriptyline hydrochloride	59358	Fluoxetine hydrochloride
24141	Amitriptyline hydrochloride	59563	Venlafaxine hydrochloride
24145	Amitriptyline hydrochloride	59593	Flupentixol dihydrochloride
24147	Amitriptyline hydrochloride	59600	Sertraline hydrochloride
24152	Amitriptyline hydrochloride	59650	Citalopram hydrobromide
24680	Amitriptyline hydrochloride	59694	Mirtazapine
24700	Iprindole	59753	Venlafaxine hydrochloride
24723	Amoxapine	59820	Amitriptyline hydrochloride
25444	Lofepramine hydrochloride	59923	Venlafaxine hydrochloride
25945	Iproniazide	59931	Trazodone hydrochloride
26016	Citalopram hydrobromide	59953	Mirtazapine
26056	Escitalopram oxalate	59954	Mirtazapine
26213	Amitriptyline hydrochloride	60138	Fluoxetine
27008	Amitriptyline hydrochloride	60355	Amitriptyline hydrochloride
27476	Iprindole	60370	Mirtazapine
27733	Iprindole	60410	Amitriptyline hydrochloride
29339	Trazodone hydrochloride	60449	Venlafaxine hydrochloride
29756	Citalopram hydrobromide	60534	Fluoxetine hydrochloride
29786	Fluoxetine hydrochloride	60538	Mirtazapine
29857	Trazodone hydrochloride	60549	Venlafaxine hydrochloride
29875	Dosulepin hydrochloride	60568	Citalopram hydrobromide
30258	Fluoxetine hydrochloride	60591	Lofepramine hydrochloride
30376	Dosulepin hydrochloride	60619	Fluoxetine hydrochloride
30983	Trazodone hydrochloride	60839	Citalopram hydrobromide
31672	Iprindole	60843	Venlafaxine hydrochloride
31824	Dosulepin hydrochloride	60888	Citalopram hydrobromide
31826	Dosulepin hydrochloride	60895	Venlafaxine hydrochloride
32121	Dosulepin hydrochloride	60929	Protriptyline hydrochloride
32401	Sertraline hydrochloride	60962	Fluoxetine hydrochloride
32439	Amitriptyline hydrochloride	61236	Venlafaxine hydrochloride
32457	Butriptyline Hydrochloride	61335	Fluoxetine hydrochloride
32546	Citalopram hydrobromide	61503	Sertraline hydrochloride
32848	Citalopram hydrobromide	61547	Mirtazapine
32863	Imipramine hydrochloride	61657	Trazodone hydrochloride
32899	Paroxetine hydrochloride	61835	Amitriptyline hydrochloride
33071	Fluoxetine hydrochloride	61842	Trazodone
33074	Imipramine hydrochloride	61856	Mirtazapine
Prodcode	**Drug Substance**	**Prodcode**	**Drug Substance**

33090	Amitriptyline hydrochloride	62155	Fluoxetine hydrochloride
33164	Dosulepin hydrochloride	62335	Fluoxetine hydrochloride
33337	Mirtazapine	62620	Clomipramine hydrochloride
33410	Fluoxetine hydrochloride	62681	Dosulepin hydrochloride
33624	Amitriptyline hydrochloride	62692	Sertraline hydrochloride
33720	Citalopram hydrobromide	62693	Sertraline hydrochloride
33779	Fluoxetine hydrochloride	62734	Venlafaxine hydrochloride
33978	Paroxetine hydrochloride	62819	Sertraline hydrochloride
34003	Trazodone hydrochloride	62927	Sertraline hydrochloride
34046	Lofepramine hydrochloride	62950	Sertraline hydrochloride
34058	Dosulepin hydrochloride	63268	Venlafaxine
34107	Amitriptyline hydrochloride	63276	Nortriptyline hydrochloride
34129	Amitriptyline hydrochloride	63403	Mirtazapine
34182	Amitriptyline hydrochloride	63441	Citalopram hydrobromide
34197	Amitriptyline hydrochloride	63481	Sertraline hydrochloride
34202	Fluoxetine hydrochloride	63859	Venlafaxine hydrochloride
34216	Fluoxetine hydrochloride	63916	Escitalopram oxalate
34222	Imipramine hydrochloride	63953	Citalopram hydrobromide
34223	Dosulepin hydrochloride	64000	Amitriptyline
34224	Amitriptyline hydrochloride	64101	Mirtazapine
34245	Clomipramine hydrochloride	64139	Mirtazapine
34251	Amitriptyline hydrochloride	64141	Amitriptyline hydrochloride
34274	Amitriptyline hydrochloride	64223	Mirtazapine
34288	Fluoxetine hydrochloride	64330	Amitriptyline hydrochloride
34294	Fluoxetine hydrochloride	64423	Citalopram hydrobromide
34351	Paroxetine hydrochloride	64458	Clomipramine hydrochloride
34355	Imipramine hydrochloride	64647	Amitriptyline hydrochloride
34356	Citalopram hydrobromide	64785	Paroxetine hydrochloride
34401	Amitriptyline hydrochloride	65152	Trazodone hydrochloride
34413	Citalopram hydrobromide	65213	Trimipramine
34415	Citalopram hydrobromide	65237	Nortriptyline hydrochloride
34419	Paroxetine hydrochloride	65439	Amitriptyline hydrochloride
34421	Trazodone hydrochloride	65445	Trimipramine maleate
34436	Citalopram hydrobromide	65482	Vortioxetine 5mg tablets
34456	Fluoxetine hydrochloride	65483	Vortioxetine 5mg tablets
34466	Citalopram hydrobromide	65555	Mirtazapine
34470	Trazodone hydrochloride	65666	Venlafaxine
34474	Amitriptyline hydrochloride	65738	Venlafaxine hydrochloride
34498	Citalopram hydrobromide	65762	Clomipramine hydrochloride
34499	Citalopram hydrobromide	65771	Sertraline
Prodcode	**Drug Substance**	**Prodcode**	**Drug Substance**

34503	Amitriptyline hydrochloride	65804	Clomipramine hydrochloride
34525	Dosulepin hydrochloride	65879	Amitriptyline hydrochloride
34578	Lofepramine hydrochloride	65899	Venlafaxine hydrochloride
34580	Trazodone hydrochloride	65987	Amitriptyline hydrochloride
34586	Citalopram hydrobromide	66100	Lofepramine hydrochloride
34587	Paroxetine hydrochloride	66183	Mirtazapine
34603	Citalopram hydrobromide	66201	Nortriptyline hydrochloride
34634	Amitriptyline hydrochloride	66292	Paroxetine hydrochloride
34641	Dosulepin hydrochloride	66413	Sertraline hydrochloride
34643	Dosulepin hydrochloride	66437	Venlafaxine hydrochloride
34672	Lofepramine hydrochloride	66493	Trimipramine maleate
34722	Citalopram hydrobromide	66560	Sertraline hydrochloride
34731	Amitriptyline hydrochloride	66572	Amitriptyline hydrochloride
34745	Dosulepin hydrochloride	66578	Amitriptyline hydrochloride
34782	Amitriptyline hydrochloride	66579	Amitriptyline hydrochloride
34813	Imipramine hydrochloride	66580	Mirtazapine
34822	Citalopram hydrobromide	66744	Fluoxetine hydrochloride
34849	Fluoxetine hydrochloride	66749	Trazodone
34856	Fluoxetine hydrochloride	66752	Mirtazapine
34866	Clomipramine hydrochloride	66890	Vortioxetine
34871	Citalopram hydrobromide	66919	Trimipramine maleate
34872	Imipramine hydrochloride	67092	Fluoxetine hydrochloride
34916	Amitriptyline hydrochloride	67097	Citalopram hydrobromide
34950	Lofepramine hydrochloride	67127	Amitriptyline hydrochloride
34966	Citalopram hydrobromide	67259	Paroxetine
34970	Citalopram hydrobromide	67271	Venlafaxine hydrochloride
35021	Paroxetine hydrochloride	67272	Mirtazapine
35112	Paroxetine hydrochloride	67288	Venlafaxine hydrochloride
35258	Doxepin hydrochloride	67431	Fluoxetine hydrochloride
35493	Doxepin hydrochloride	67496	Fluoxetine hydrochloride
36746	Citalopram hydrobromide	67562	Fluoxetine hydrochloride
36893	Fluoxetine hydrochloride	67563	Venlafaxine hydrochloride
37256	Fluoxetine hydrochloride	67728	Dosulepin hydrochloride
38274	Clomipramine hydrochloride	67730	Sertraline hydrochloride
38890	Fluoxetine hydrochloride	67736	Fluoxetine hydrochloride
39145	Nortriptyline Hydrochloride	67742	Lofepramine hydrochloride
39359	Venlafaxine Hydrochloride	67758	Fluoxetine hydrochloride
39360	Venlafaxine Hydrochloride	67769	Fluoxetine hydrochloride
39770	Venlafaxine hydrochloride	67874	Vortioxetine
39809	Venlafaxine hydrochloride	67888	Fluoxetine hydrochloride
Prodcode	**Drug Substance**	**Prodcode**	**Drug Substance**

40048	Venlafaxine hydrochloride	67928	Sertraline hydrochloride
40049	Venlafaxine hydrochloride	67935	Imipramine hydrochloride
40054	Venlafaxine Hydrochloride	67990	Dosulepin hydrochloride
40059	Venlafaxine Hydrochloride	68050	Venlafaxine hydrochloride
40062	Venlafaxine Hydrochloride	68052	Mirtazapine
40092	Venlafaxine hydrochloride	68228	Nortriptyline
40160	Mirtazapine	68266	Fluoxetine hydrochloride

Appendix 3 Fall Identification Codes

Table 3.1 – Read Codes for Fall

Read Code	Code Description
16D..00	FALLS
16D1.00	RECURRENT FALLS
R200.12	[D] GERIATRIC FALL
TC...00	ACCIDENTAL FALLS
TC...11	FALL - ACCIDENTAL
TC0..00	FALL ON OR FROM STAIRS OR STEPS
TC00.00	FALL ON OR FROM ESCALATOR
TC00000	FALL ON ESCALATOR
TC01.00	FALL ON OR FROM STAIRS
TC01000	FALL ON STAIRS
TC01100	FALL FROM STAIRS
TC01z00	FALL ON OR FROM STAIRS NOS
TC02.00	FALL ON OR FROM STEPS
TC02000	FALL ON STEPS
TC02100	FALL FROM STEPS
TC02z00	FALL ON OR FROM STEPS NOS
TC0z.00	FALL ON OR FROM STAIRS OR STEPS NOS
TC1..00	FALL ON OR FROM LADDERS OR SCAFFOLDING
TC10.00	FALL FROM LADDER
TC11.00	FALL FROM SCAFFOLDING
TC2..00	FALL FROM OR OUT OF BUILDING OR OTHER STRUCTURE
TC20.00	FALL FROM BALCONY
TC21.00	FALL FROM BRIDGE
TC22.00	FALL FROM BUILDING
TC27.00	FALL FROM WALL
TC28.00	FALL FROM WINDOW
TC29.00	FALL THROUGH ROOF
TC2z.00	FALL FROM OR OUT OF BUILDING OR OTHER STRUCTURE NOS
TC3..00	FALL INTO HOLE OR OTHER OPENING IN SURFACE
TC30.00	ACCIDENT CAUSED BY DIVING OR JUMPING INTO WATER
TC31.00	ACCIDENTAL FALL INTO WELL
TC32.00	ACCIDENTAL FALL INTO MANHOLE
TC32000	ACCIDENTAL FALL INTO MANHOLE, UNSPECIFIED
TC3y.00	FALL INTO OTHER HOLE OR OTHER OPENING IN SURFACE
TC3y100	FALL INTO DOCK
TC3y200	FALL INTO HOLE
TC3y300	FALL INTO PIT
TC3y400	FALL INTO QUARRY
TC3y600	FALL INTO TANK

Read Code	Code Description
TC3y600	FALL INTO TANK
TC3yz00	FALL INTO OTHER HOLE, UNSPECIFIED
TC3z.00	FALL INTO HOLE NOS
TC4..00	OTHER FALL FROM ONE LEVEL TO ANOTHER
TC40.00	FALL FROM PLAYGROUND EQUIPMENT
TC41.00	FALL FROM CLIFF
TC42.00	FALL FROM CHAIR OR BED
TC42000	FALL FROM CHAIR
TC42100	FALL FROM BED
TC42z00	FALL FROM CHAIR OR BED NOS
TC4y.00	OTHER FALL FROM ONE LEVEL TO ANOTHER
TC4y100	FALL FROM HAYSTACK
TC4y200	FALL FROM STATIONARY VEHICLE
TC4y300	FALL FROM TREE
TC4yz00	OTHER FALL FROM ONE LEVEL TO ANOTHER NOS
TC4z.00	FALL FROM ONE LEVEL TO ANOTHER NOS
TC5..00	FALL ON SAME LEVEL FROM SLIPPING, TRIPPING OR STUMBLING
TC50.00	FALL ON SAME LEVEL FROM SLIPPING
TC51.00	FALL ON SAME LEVEL FROM TRIPPING
TC52.00	FALL ON SAME LEVEL FROM STUMBLING
TC5z.00	FALL ON SAME LEVEL FROM SLIPPING, TRIPPING OR STUMBLING NOS
TC6..00	FALL ON SAME LEVEL- COLLISION/PUSH/SHOVE BY/WITH OTH PERSON
TC60.00	FALL ON SAME LEVEL FROM SPORTS CONTACT
TC60000	FALL ON SAME LEVEL FROM TACKLE IN SPORT
TC60y00	OTHER FALL IN SPORT
TC60z00	FALL ON SAME LEVEL FROM SPORTS CONTACT NOS
TC6y000	FALL ON SAME LEVEL FROM COLLISION WITH OTHER PERSON, UNSPEC
TC6y100	FALL ON SAME LEVEL FROM PUSHING BY OTHER PERSON, UNSPECIFIED
TC6y200	FALL ON SAME LEVEL FROM SHOVING BY OTHER PERSON, UNSPECIFIED
TC6yz00	OTHER FALL ON SAME LEVEL- PUSH/SHOVE/COLLIDE-OTH PERSON NOS
TC6z.00	FALL ON SAME LEVEL- PUSH/SHOVE/COLLIDE - OTHER PERSON NOS
TCy..00	OTHER FALLS
TCy0.00	FALL FROM BUMP AGAINST OBJECT
TCyz.00	OTHER ACCIDENTAL FALL NOS
TCz..00	ACCIDENTAL FALLS NOS
U10..00	[X]FALLS
U100.00	[X]FALL ON SAME LEVEL INVOLVING ICE AND SNOW

Read Code	Code Description
U100000	[X]FALL ON SAME LEVEL INVOLVING ICE AND SNOW OCCURRN HOME
U100300	[X]FALL SAME LEVL INVOLV ICE/SNOW, OCC SPORT/ATHLET AREA
U100400	[X]FALL SAME LEVL INV ICE AND SNOW, OCC STREET / HIGHWAY
U100500	[X]FALL SAME LEVL INV ICE / SNOW, OCC TRADE / SERVICE AREA
U100z00	[X]FALL SAME LEVL INV ICE / SNOW, OCC AT UNSPECIFIED PLACE
U101.00	[X]FALL ON SAME LEVEL FROM SLIPPING, TRIPPING AND STUMBLING
U101000	[X]FALL SAME LEVL FRM SLIP TRIP + STUMB, OCCURRENCE AT HOME
U101100	[X]FALL SAME LEVEL FROM SLIP TRIP + STUMB OCC RESID INSTIT
U101200	[X]FALL SME LEVL SLP TRP+STMB OCC SCH, OTH INST/PUB ADM AREA
U101300	[X]FALL SME LEVL FRM SLIP TRIP+STUMB, OCC SPORT/ATHLET AREA
U101400	[X]FALL SAME LEVEL FROM SLIP TRIP+STUMB, OCC STREET/HIGHWAY
U101500	[X]FALL SME LVL FRM SLIP TRIP+STUMB, OCC TRADE/SERVICE AREA
U101600	[X]FALL SAME LEVL, SLIP TRIP+STUMB OCC INDUST/CONSTRUCT AREA
U101700	[X]FALL SAME LEVEL FROM SLIP TRIP+STUMBLING, OCCUR ON FARM
U101y00	[X]FALL SAME LEVEL, SLIP TRIP+STUMB, OCC OTHER SPECIF PLACE
U101z00	[X]FALL SAME LEVL FRM SLIP TRIP+STUMBLING, OCC UNSPEC PLACE
U102.00	[X]FALL INVOLV ICE-SKATES SKIS ROLLER-SKATES OR SKATEBOARDS
U102000	[X]FALL INV ICE-SKATE SKIS ROLL-SKATE/SKATEBOARD, OCC HOME
U102300	[X]FALL INV ICE-SKT SKI ROL-SKT/SKBRD OCC SPORT/ATHLET AREA
U102400	[X]FALL INV ICE-SKAT SKI ROLL-SKAT/SKBRD OCC STREET/HIGHWAY
U102700	[X]FALL INV ICE-SKAT SKI ROLL-SKAT/SKATEBRD, OCCUR ON FARM
U102z00	[X]FALL INV ICE-SKAT SKI ROLL-SKAT/SKBRD OCC UNSPECIF PLACE
U103.00	[X]OTH FALL SAME LEVL DUE COLLISN/PUSHING BY ANOTHER PERSON
U103000	[X]OTH FALL SAME LEVL, COLLISN/PUSH BY ANOTH PERS, OCC HOME
U103300	[X]OTH FALL SME LEVL COL/PUSH ANOTH PERS OCC SPORT/ATHL AREA
U103y00	[X]OTH FALL SME LEVL COLL/PUSH ANOTH PER OCC OTH SPEC PLACE
U103z00	[X]OTH FALL SAME LEVL COLL/PUSH ANOTH PERS OCC UNSPEC PLACE
U104.00	[X]FALL WHILE BEING CARRIED OR SUPPORTED BY OTHER PERSONS

Read Code	Code Description
U104100	[X]FALL WHLE CARRIED/SUPPORTED OTH PERSONS OCC RESID INSTIT
U104600	[X]FALL WHLE CARR'D/SUPPRTD OTH PERS OCC INDUST/CONSTR AREA
U105.00	[X]FALL INVOLVING WHEELCHAIR
U105100	[X]FALL INVOLVNG WHEELCHAIR OCCURRENCE RESIDENTIAL INSTIT'N
U105500	[X]FALL INVOLVNG WHEELCHAIR OCCURRNCE AT TRADE/SERVICE AREA
U106.00	[X]FALL INVOLVING BED
U106000	[X]FALL INVOLVING BED, OCCURRENCE AT HOME
U106100	[X]FALL INVOLVING BED OCCURRENCE IN RESIDENTIAL INSTITUTION
U107.00	[X]FALL INVOLVING CHAIR
U107000	[X]FALL INVOLVING CHAIR, OCCURRENCE AT HOME
U107200	[X]FALL INVLV CHAIR OCC AT SCHOOL OTH INSTIT/PUB ADMIN AREA
U107600	[X]FALL INVOLVING CHAIR OCCURRENCE AT INDUST/CONSTRUCT AREA
U107z00	[X]FALL INVOLVING CHAIR, OCCURRENCE AT UNSPECIFIED PLACE
U108.00	[X]FALL INVOLVING OTHER FURNITURE
U108000	[X]FALL INVOLVING OTHER FURNITURE, OCCURRENCE AT HOME
U108100	[X]FALL INVOLV OTHER FURNITURE OCCURRN RESIDENT INSTITUT'N
U108600	[X]FALL INVOLV OTH FURNITRE OCCURRNCE AT INDUST/CONSTR AREA
U109.00	[X]FALL INVOLVING PLAYGROUND EQUIPMENT
U109000	[X]FALL INVOLVING PLAYGROUND EQUIPMENT, OCCURRENCE AT HOME
U109200	[X]FALL INV PLAYGRND EQUIP OCC SCH OTH INST/PUB ADMIN AREA
U109z00	[X]FALL INVOLV PLAYGRND EQUIPM OCCURRNCE AT UNSPECIF PLACE
U10A.00	[X]FALL ON AND FROM STAIRS AND STEPS
U10A000	[X]FALL ON AND FROM STAIRS AND STEPS, OCCURRENCE AT HOME
U10A100	[X]FALL ON + FROM STAIR + STEP OCCURRNCE RESIDENT INSTIT'N
U10A500	[X]FALL ON + FROM STAIR + STEP OCCURRN AT TRADE/SERVCE AREA
U10A511	[X]FALL ON OR FROM ESCALATOR
U10Ay00	[X]FALL ON + FROM STAIR + STEP OCCURRN AT OTH SPECIF PLACE
U10Az00	[X]FALL ON + FROM STAIR + STEP OCCURRNCE AT UNSPECIF PLACE
U10B.00	[X]FALL ON/FROM LADDER
U10B000	[X]FALL ON AND FROM LADDER, OCCURRENCE AT HOME
U10By00	[X]FALL ON+FROM LADDER, OCCURRENCE AT OTHER SPECIFIED PLACE

Read Code	Code Description
U10C600	[X]FALL ON+FROM SCAFFOLD OCCURRN AT INDUSTR/CONSTRUCTN AREA
U10D.00	[X]FALL FROM, OUT OF OR THROUGH BUILDING OR STRUCTURE
U10D000	[X]FALL FROM OUT OF/THROUGH BUILDING/STRUCTUR OCCURN HOME
U10D300	[X]FALL FRM OUT/THRO BLDNG/STRUCT OCC AT SPORT/ATHLET AREA
U10D600	[X]FALL FROM OUT/THRO BUILDNG/STRUCT OCC INDUST/CONSTR AREA
U10E.00	[X]FALL FROM TREE
U10E000	[X]FALL FROM TREE, OCCURRENCE AT HOME
U10Ez00	[X]FALL FROM TREE, OCCURRENCE AT UNSPECIFIED PLACE
U10F000	[X]FALL FROM CLIFF, OCCURRENCE AT HOME
U10F300	[X]FALL FROM CLIFF, OCCURRENCE AT SPORTS AND ATHLETICS AREA
U10G.00	[X]DIV'G/JUMP'G INTO WATER CAUS INJ OTH THAN DROWN'G/SUBM'N
U10G300	[X]DIV/JMP WATR CAUS INJ OTH THN DRWN/SUBM, SPRT/ATHLET AREA
U10G600	[X]DIV/JMP WATR CAUS INJ OTH THN DRWN/SUBM OCC INDUS AREA
U10H.00	[X]OTHER FALL FROM ONE LEVEL TO ANOTHER
U10H000	[X]OTHER FALL FROM ONE LEVEL TO ANOTHER, OCCURRENCE AT HOME
U10H200	[X]OTHR FALL FRM ONE LEVEL TO ANOTHR, SCH INST/PUB ADM AREA
U10H300	[X]OTHR FALL FROM ONE LEVEL TO ANOTHR OCC SPORT/ATHLET AREA
U10H400	[X]OTHR FALL FROM ONE LEVEL TO ANOTHR OCCURRN STREET/H'WAY
U10H500	[X]OTHER FALL FRM ONE LEVEL TO ANOTHR OCC AT TRDE/SERV AREA
U10Hy00	[X]OTHER FALL FRM ONE LEVL TO ANOTHR OCC AT OTH SPECIF PLCE
U10Hz00	[X]OTHR FALL FRM ONE LEVEL TO ANOTHR OCCURRN AT UNSPEC PLCE
U10J.00	[X]OTHER FALL ON SAME LEVEL
U10J000	[X]OTHER FALL ON SAME LEVEL, OCCURRENCE AT HOME
U10J300	[X]OTHER FALL ON SAME LEVEL OCCURRN AT SPORTS/ATHLETIC AREA
U10J600	[X]OTHER FALL ON SAME LEVL, OCCURRN AT INDUST/CONSTUCT AREA
U10z.00	[X]UNSPECIFIED FALL
U10z000	[X]UNSPECIFIED FALL, OCCURRENCE AT HOME
U10z100	[X]UNSPECIFIED FALL, OCCURRENCE IN RESIDENTIAL INSTITUTION
U10z300	[X]UNSPECIFIED FALL, OCCURRENCE AT SPORTS / ATHLETICS AREA
U10z600	[X]UNSPECIFIED FALL OCCURRN AT INDUSTRIAL/CONSTRUCTION AREA
U10zz00	[X]UNSPECIFIED FALL, OCCURRENCE AT UNSPECIFIED PLACE

Appendix 3 Table 3.2 – ICD Codes for Falls

ICD-10 Code	Description
W01	Fall on same level from slipping, tripping and stumbling
W02	Fall involving ice-skates, skis, roller-skates or skateboards
W03	Other fall on same level due to collision with, or pushing by, another person
W04	Fall while being carried or supported by other persons
W05	Fall involving wheelchair
W06	Fall involving bed
W07	Fall involving chair
W08	Fall involving other furniture
W09	Fall involving playground equipment
W10	Fall on and from stairs and steps
W11	Fall on and from ladder
W12	Fall on and from scaffolding
W13	Fall from, out of or through building or structure
W14	Fall from tree
W15	Fall from cliff
W16	Diving or jumping into water causing injury other than drowning or submersion
W17	Other fall from one level to another
W18	Other fall on same level
W19	Unspecified fall

Appendix 4 Kaplan Meier's Graphs of Analgesic Use within the First 6 Months of KOA diagnosis

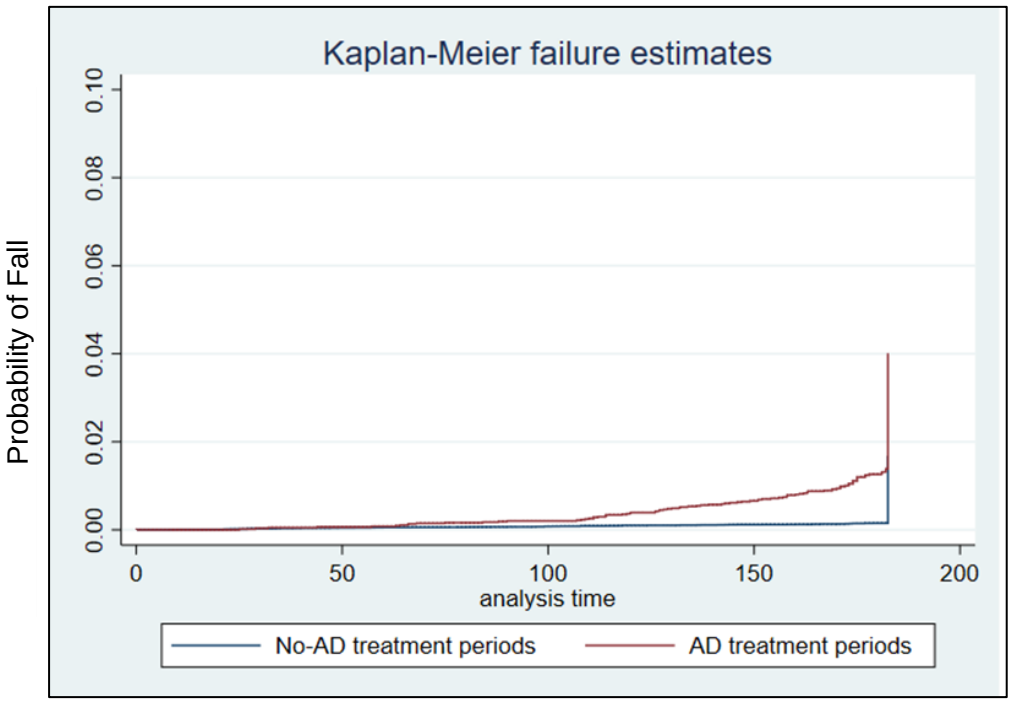

Figure A4-1 Kaplan-Meier failure estimates for current use of Antidepressants (AD)

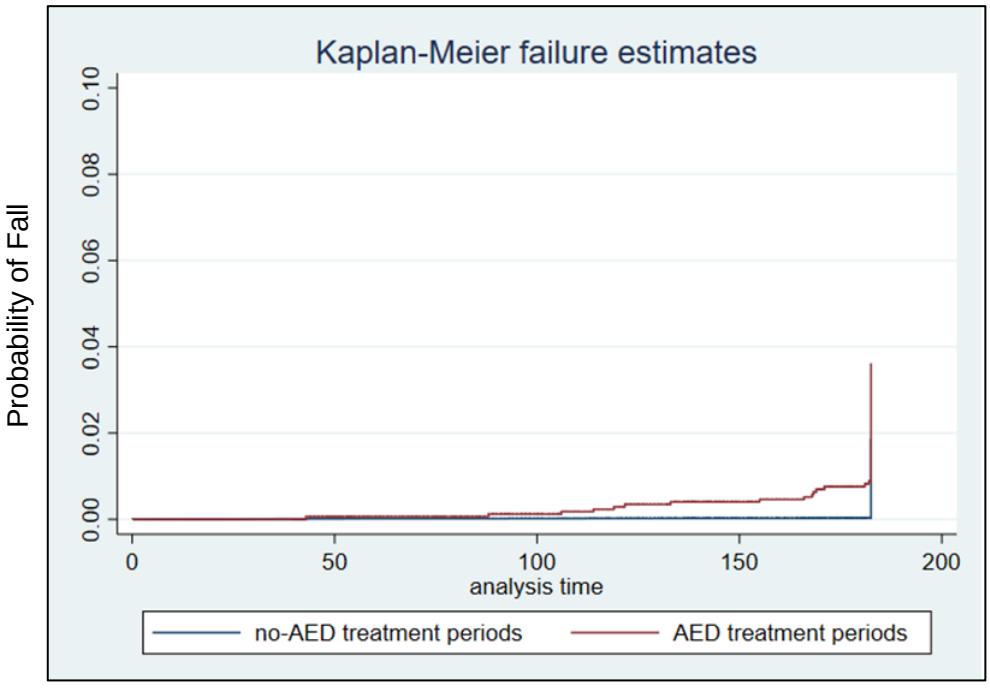

Figure A4-2 Kaplan-Meier failure estimates for current use of Anti-Epileptic Drugs (AED)

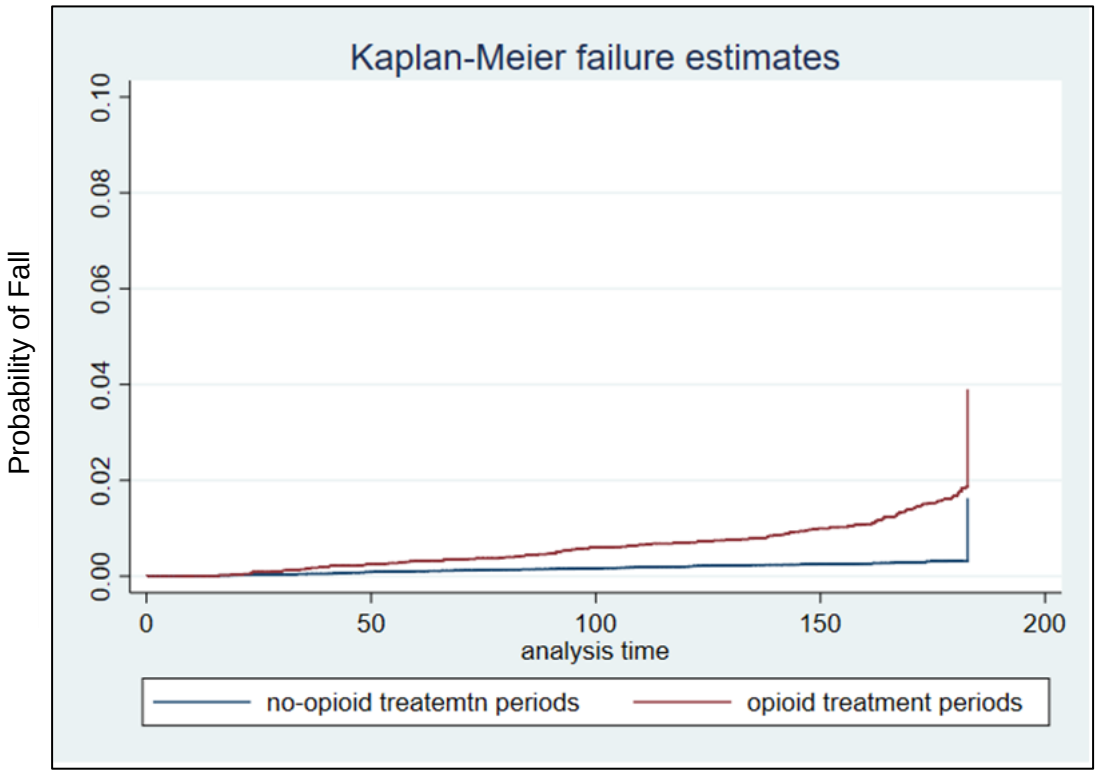

Figure A4-3 Kaplan-Meier failure estimates for current use of opioids

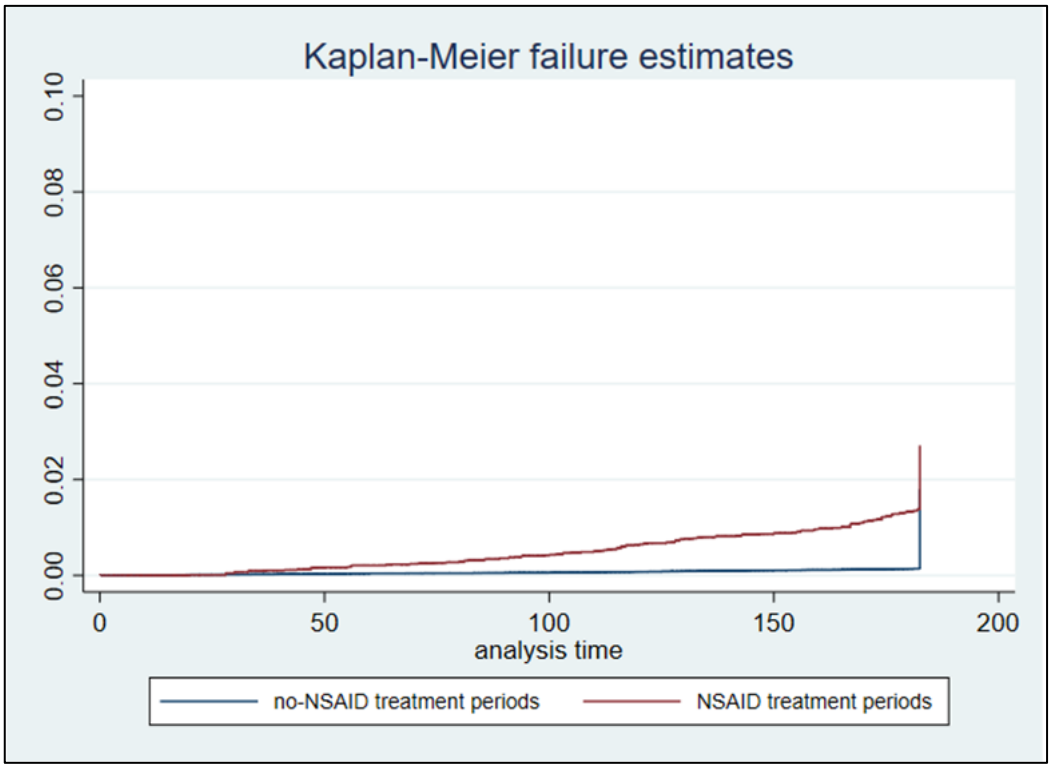

Figure A4-4 Kaplan-Meier failure estimates for current use of Non-Steroidal Anti-Inflammatory Drugs (NSAID)

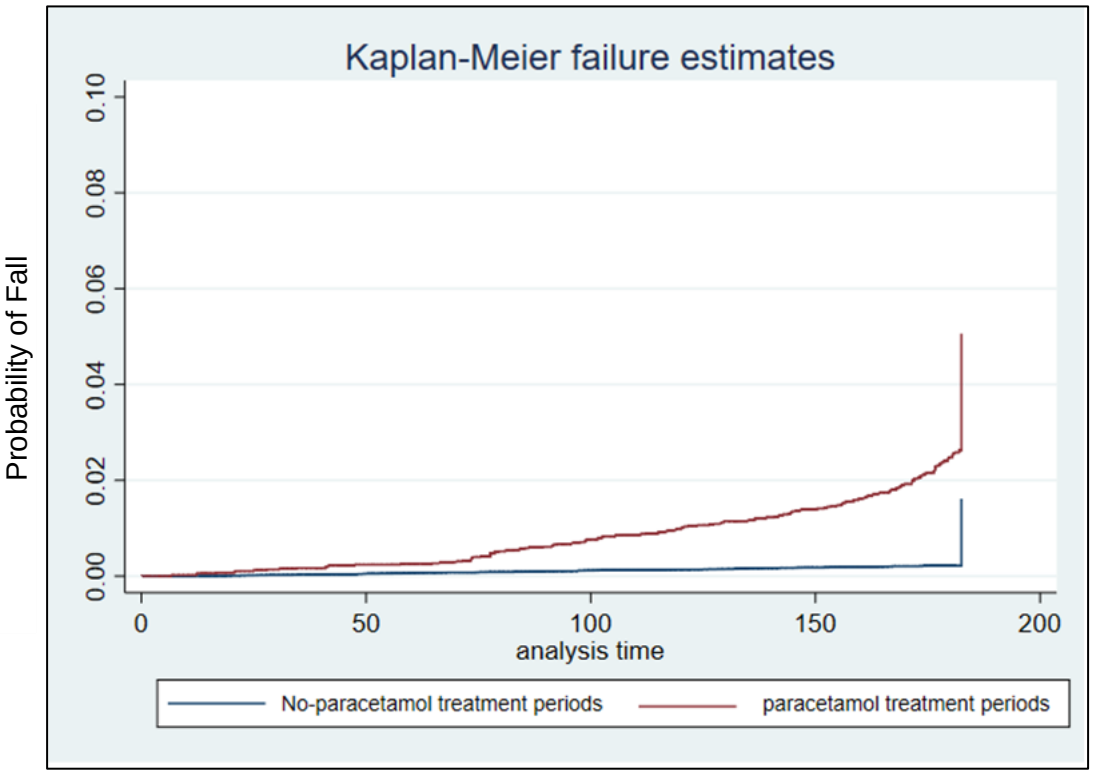

Figure A4-5 Kaplan-Meier failure estimates for current use of paracetamol

Appendix 5 Kaplan Meier's Graphs of Analgesic Use within the

<u>Second 6- months</u> of KOA diagnosis

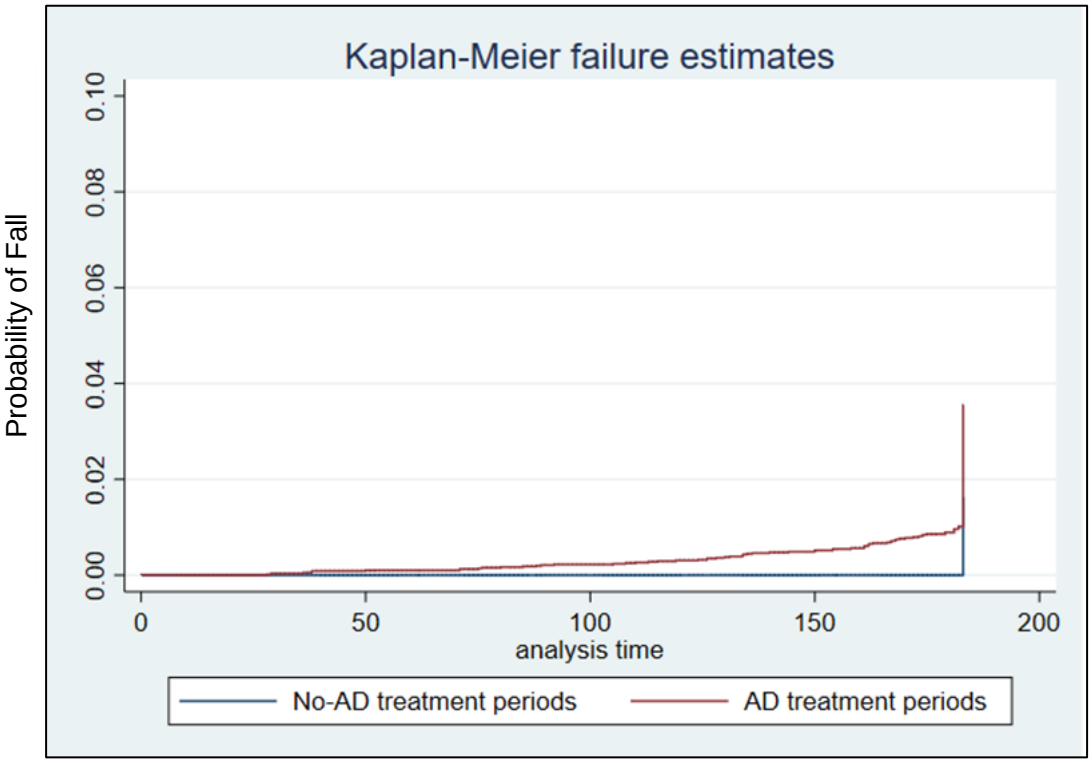

Figure A5-1 Kaplan-Meier failure estimates for current use of Antidepressants (AD)

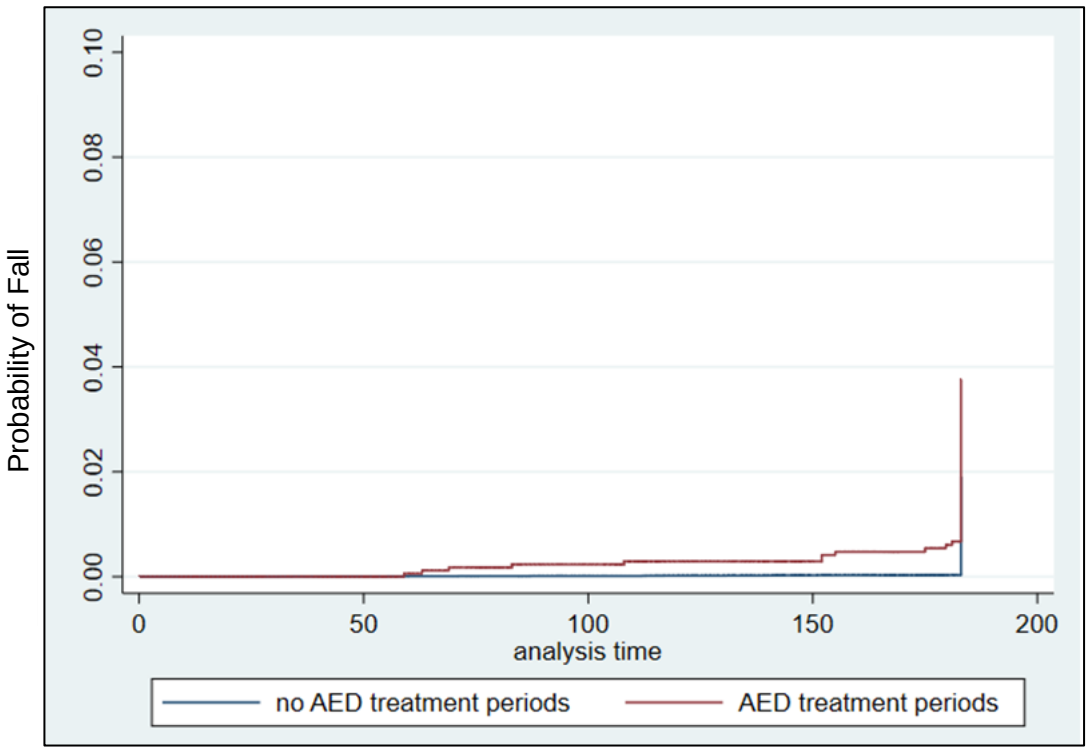

Figure A5-2 Kaplan-Meier failure estimates for current use of Anti-Epileptic Drugs (AED)

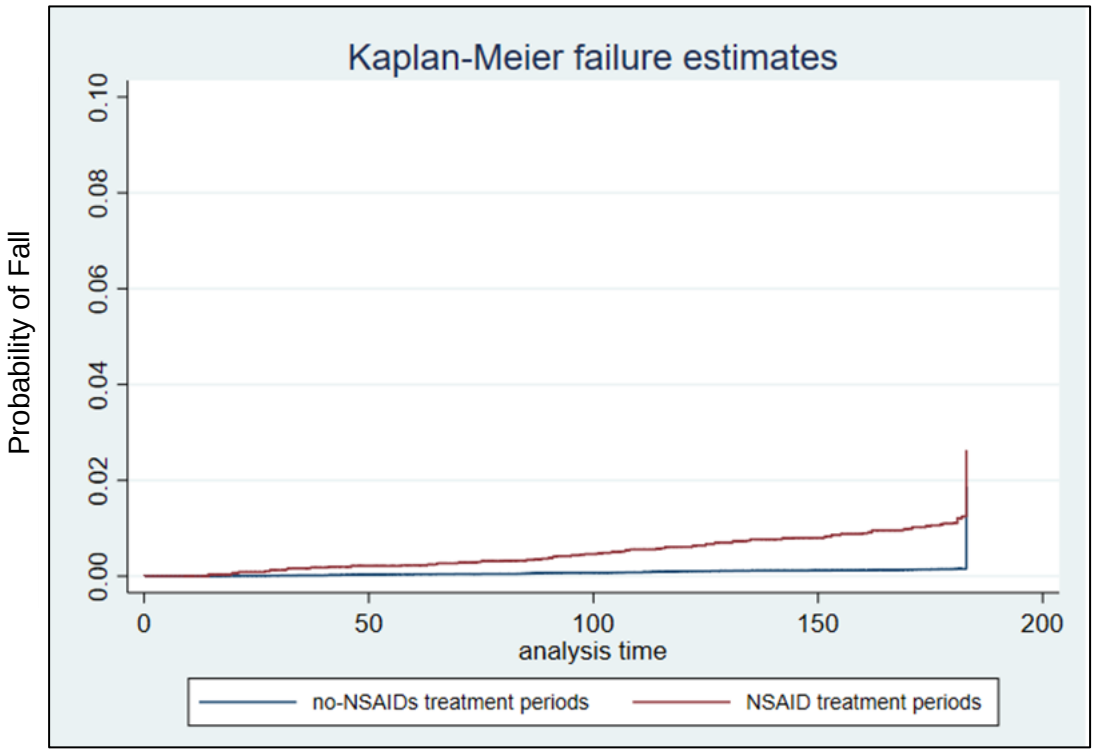

Figure A5-3 Kaplan-Meier failure estimates for current use of Non-Steroidal Anti-Inflammatory Drugs (NSAID)

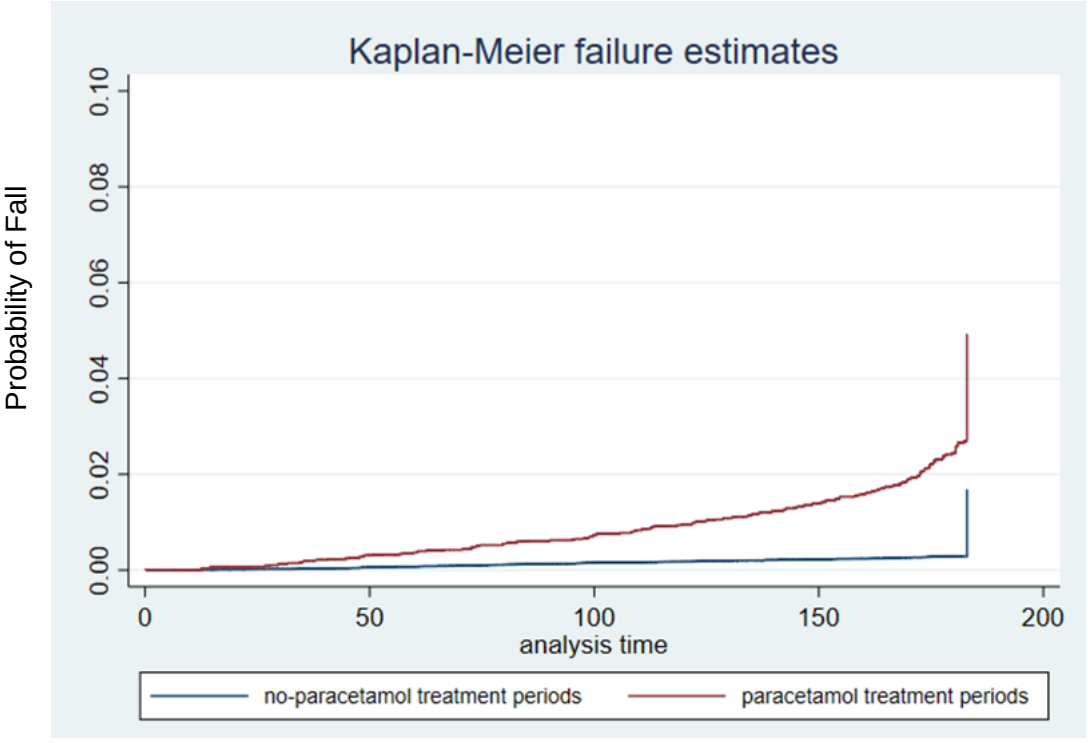

Figure 5-4 Kaplan-Meier failure estimates for current use of Paracetamol

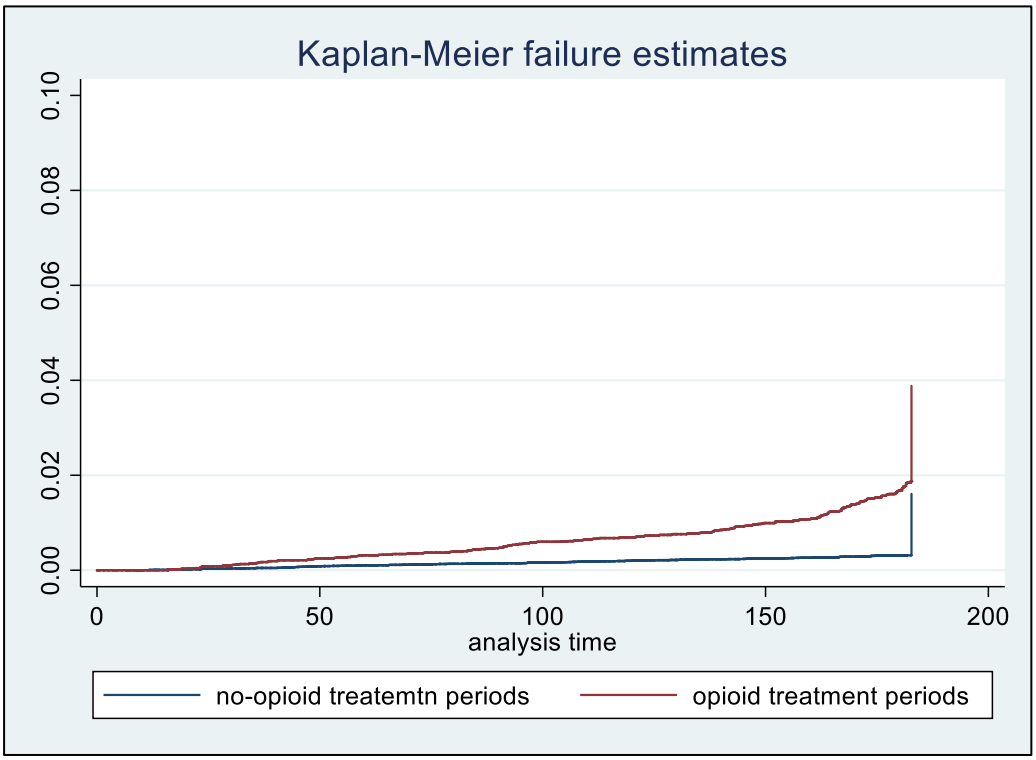

Figure A5-5 Kaplan-Meier failure estimates for current use of Opioids (OP)

Appendix 6 Cumulative Doses of Analgesics

Table A6-1 Number and proportion of **AED users** stratified by cumulative doses prescribed during the first year after AED Initiation

Number of Patients	Total	Older AEDs	Newer AEDs	Older + Newer
N (row %)	13,257	2,470 (18.6)	10,308 (77.8)	479 (3.6)
Cumulative dose DDD/patient/year, n (column %)				
<30	5,171 (39.0)	676 (27.4)	4,412 (42.8)	83 (17.3)
30–90	2,709 (20.4)	415 (16.8)	2,193 (21.3)	101 (21.0)
91–180	2,219 (16.8)	512 (20.7)	1,634 (15.8)	73 (15.2)
>180	3,158 (23.8)	867 (35.1)	2,069 (20.1)	222 (46.5)

AED anti-epileptic drugs DDD defined daily dose Older + Newer:used both during the first year of AED initiation.

Table A6-2 Number and proportion of **opioid users** stratified by cumulative doses prescribed during the first year after opioid Initiation

Number of Patients	Total	Weak	Strong	Strong + Weak
N (row %)	75,977	56,628 (74.5)	7,040 (9.3)	12,309 (16.2)
Cumulative dose DDD/patient/year, n (column %)				
<30	34,880 (45.9)	29,795 (52.6)	3,295 (46.8)	1,790 (14.5)
30–90	19,497 (25.6)	14,113 (24.9)	1,470 (20.9)	3,914 (31.8)
91–180	10,255 (13.5)	6,509 (11.5)	985 (14.0)	2,761 (22.4)
>180	11,345 (15.0)	6,211 (11.0)	1,290 (18.3)	3,844 (31.3)

DDD defined daily dose. Strong + Weak:used both weak and strong opioids in the first year of opioid initiation.

Table A6-3 Number and proportion of **NSAID users** stratified by cumulative doses prescribed during the first year after NSAID Initiation

Number of Patients	**Total**	**Non-selective**	**COX-2 Inhibitors**	**Non-selective + COX-2 Inhibitors**
N (row %)	53,809	42,569 (79.1)	3,300 (6.2)	7,940 (14.7)
Cumulative dose DDD/patient/year, n (column %)				
<30	14,270 (26.5)	13,109 (30.7)	543 (16.5)	618 (7.8)
30–90	17,564 (32.6)	14,235 (33.4)	1,208 (36.6)	2,121 (26.6)
91–180	7,440 (13.8)	5,638 (13.2)	406 (12.3)	1,396 (17.5)
>180	14,535 (27.0)	9,587 (22.5)	1143 (34.6)	3,805 (47.9)

COX-2 cyclo-oxygenase inhibitor DDD defined daily dose Non-selective + COX-2 Inhibitors:were prescribed both non-selective as well well as COX-2 inhibitors within the first year after opioid initiation.

Table A6-4 Number and proportion of **paracetamol users** stratified by cumulative doses prescribed during the first year after paracetamol Initiation

Cumulative Dose DDD/Patient/Year	**Number of Patients n=65,350 (%)**
<30	21,322 (32.6)
30–90	19,713 (30.2)
91–180	12,884 (19.7)
>180	11,431 (17.5)

DDD defined daily doses

Appendix 7 Charactaristics of Persistent Analgesic Users

Table A7-1 Characteristics of AED users by persistence of use

Number of Patients n= 13,257 (% From Total Users)	**Pattern of AED use**	
	Persistent	Non-persistent
	3,157 (23.8)	10,100 (76.2)
Demographic and clinical characteristics (% of total respective use pattern)		
Mean age, years (SD)	62.9 (13.03)	69.0 (12.42)
Age ranks, years		
<40	112 (3.5)	125 (1.2)
40–64	1,565(49.6)	3,306 (32.7)
65–80	1,167 (37.0)	4,568 (45.3)
>80	313 (9.9)	2,101 (20.8)
Gender (% of total respective use pattern)		
Males	1,240 (39.3)	3,320 (32.8)
Females	1,917 (60.7)	6,780 (67.2)
Comorbidity	1,059 (33.5)	2,144 (21.2)
Prescription data (% of total respective use pattern)		
Amount of AED DDD/patient/year Median (IQR)	296.6 (222.6,400)	28 (10,8.8)
Number of prescriptions per year, Median (IQR)	13 (10,16)	3 (1,8)

AED: antiepileptic drugs; IQR: inter quartile range; DDD: defined daily doses SD standard deviation

Table A7-2 Characteristics of opioid users by persistence of use

Number of Patients n= 75,977 (% From Total Users)	**Pattern of Opioid Use**	
	Persistent	Non-persistent
	11,345 (14.9)	64,632 (85.1)
Demographic and clinical characteristics (% of total respective use pattern)		
Mean age, years (SD)	64.6 (12.46)	68.0 (12.36)
Age ranks, years		
<40	269 (2.3)	856 (1.3)
40–64	5,271 (46.5)	23,283 (36.0)
65–80	4,422 (39.0)	28,835 (44.6)
>80	1,383 (12.2)	11,658 (18.1)
Gender (% of total respective use pattern)		
Males	4,161 (36.7)	25,121 (38.9)
Females	7,184 (63.3)	39,511 (61.1)
Recorded comorbidity	2,200 (19.4)	10,499 (16.2)
Prescription data (% of total respective use pattern)		
Amount of opioids DDD/patient/year Median (IQR)	285 (225, 401.5)	25 (11.2, 113.3)
Number of prescriptions per year, Median (IQR)	14 (11,19)	2 (1,6)

IQR: inter quartile range; DDD: defined daily doses SD standard deviation

Table A7-3 Characteristics of NSAID users by persistence of use

Number of patients n= 53,809 (% from total users)	**Pattern of NSAID use**	
	Persistent	Non-persistent
	14,524 (27.0)	39,285 (73.0)
Demographic and clinical characteristics (% of total respective use pattern)		
Mean age, years (SD)	64.6 (11.26)	65.4 (12.6)
Age ranks, years		
<40	187(1.3)	907 (2.3)
40–64	6,996 (48.2)	16,937(43.1)
65–80	5,990 (41.2)	16,303(41.5)
>80	1,351 (9.3)	5,138 (13.0)
Gender		
Males	5,794 (39.9)	15,769 (40.1)
Females	8,730 (60.9)	23,516 (59.9)
Comorbidity	2,236 (15.4)	5,773 (14.7)
Prescription data (% of total respective use pattern)		
Amount of NSAID DDD/patient/year Median (IQR)	330 (252,419)	42 (28,84)
Number of prescriptions per years, Median (IQR)	9 (7,11.5)	1(1,3)

NSAIDs Non-steroidal anti-inflammatory drugs IQR: inter quartile range; DDD: defined daily doses SD standard deviation

Table A7-4 Characteristics of paracetamol users by persistence of use

Number of Patients n= 65,350(%)	**Pattern of Paracetamol Use**	
	Persistent	Non-persistent
	11,431 (17.5)	53,919 (82.5)
Demographic and clinical characteristics (% of total respective use pattern)		
Mean age, years (SD)	71.9 (11.75)	69.8 (11.86)
Age ranks, years		
<40	67(0.6)	507(0.9)
40–64	2,804 (24.5)	16,151(30.0)
65–80	5,464(47.8)	25,921(48.1)
>80	3,096(27.1)	11,340 (21.0)
Gender		
Males	3,697 (32.3)	20,145 (37.4)
Females	7,734 (67.7)	33,774 (62.6)
Comorbidity	2,277 (19.9)	9,184 (17.0)
Prescription data (% of total respective use pattern)		
Amount of paracetamol DDD/patient/year Median (IQR)	233.3 (200,316.6)	33.3 (16.6,83.3)
Number of prescriptions per year, Median (IQR)	13 (11,16)	6(3,9)

IQR: inter quartile range; DDD: defined daily doses SD standard deviation

Appendix 8 Kaplan Meier's Failure Estimates for Analgesic Users

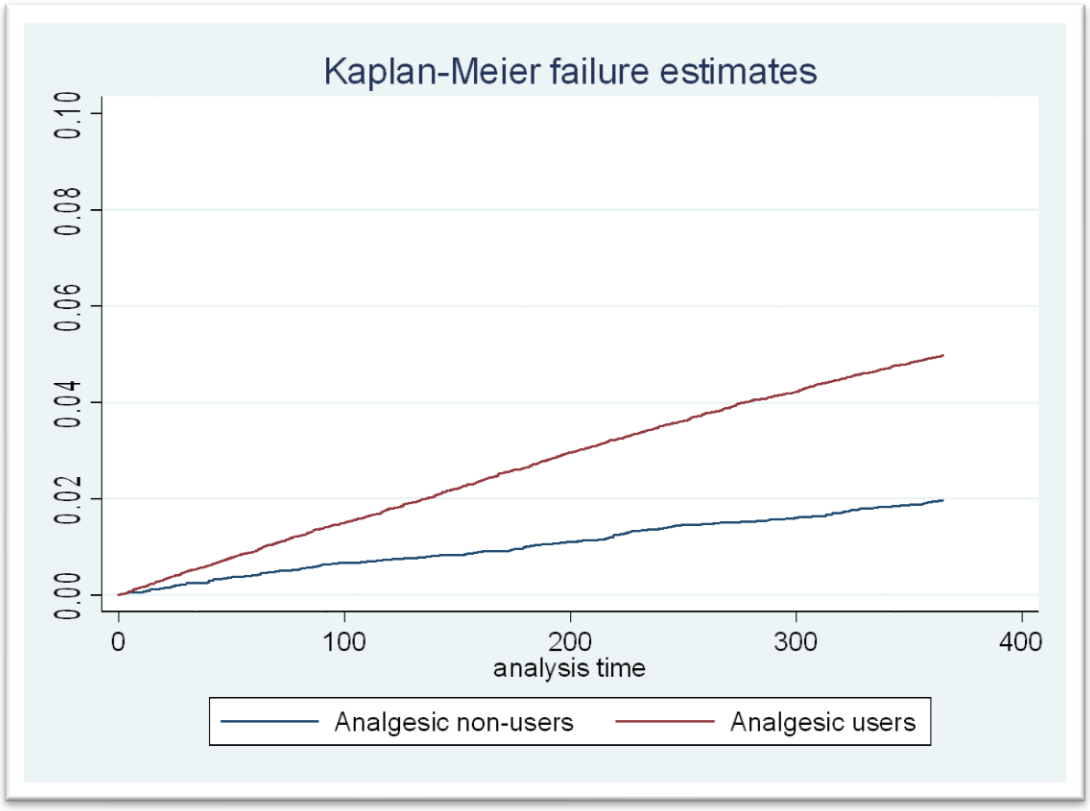

Figure A8-1 Kaplan Meier Survival Estimates Among Analgesic Treatment Users and Non-users

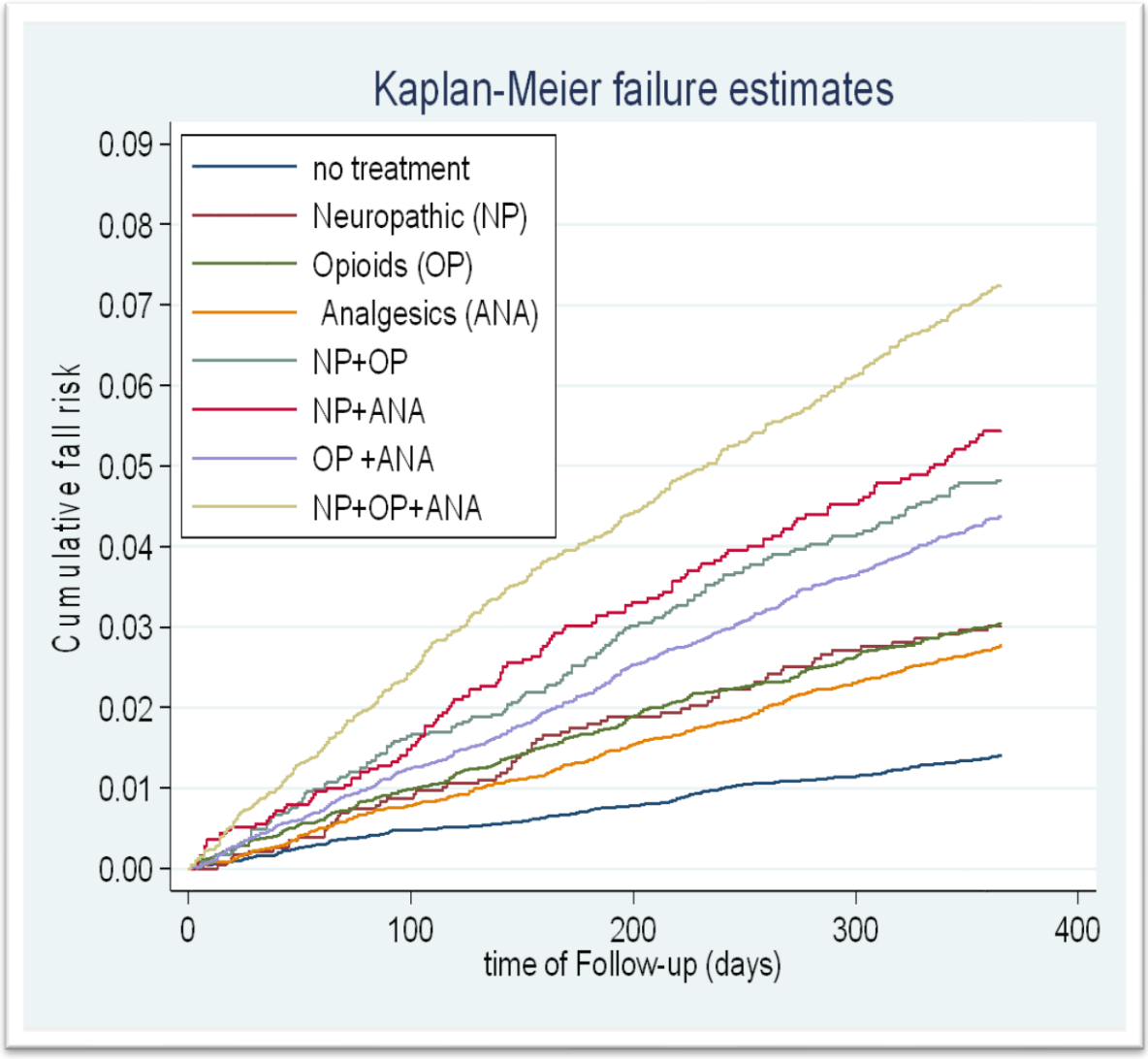

Figure A8-2 Survival Function for the Different Analgesic Treatment Groups.